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SEARCH REQUEST FORM

Requestor's Name: Natalie Davis Serial Number: 09/756978

Date: 10-16-01 Phone: 308-6410 Art Unit: 164

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alleviating a tumor by administering interferon-gamma and a type 1 inflammatory response promoting agent + an antigen releasing agent.

A. The antigen releasing agent comprises a proteolytic enzyme ~~(see claim 18)~~ (claims 4-9)

B. The inflammatory response agent as in claims 29.

Key claims 1, 3, 9, 18, 22 & 29

STAFF USE ONLY

Date completed:
Searcher: ~~Alex Weglawiw~~
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Elapsed time:
CPU time:
Total time: 21
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Point of Contact:
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D.U. 10-25-01

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- ____ DARC/Questel
- ____ Other

0 30
7 12
4 8
+ 12
60

PTO-1590 (9-90)
USCOMM-DC 90-3952
★ U.S. GPO: 1995-398-798/22489

W. Davis
756978

```
=> fil medl,caplus,biosis,embase,wpids,jicst
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.65       0.80

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=> e interferon+all/ct
'ALL' IS NOT VALID HERE
ADDITIONAL TERMS AVAILABLE BY USING "INTERFERON+XUSE/CT"
E#   FREQUENCY    AT     TERM
--   ---------    --     ----
E1           3            INTERFEROMETRY: SN, STATISTICS & NUMERICAL DATA/CT
E2           4            INTERFEROMETRY: ST, STANDARDS/CT
E3       32242    63 --> INTERFERON/CT
E4           9            INTERFERON (IFN)/CT
E5           1            INTERFERON (IFN, INTRON A)/CT
E6           2            INTERFERON (INFERGEN)/CT
E7           2            INTERFERON (INTRON A)/CT
E8           1            INTERFERON (INTRON)/CT
E9        1336     2      INTERFERON .ALPHA./CT
E10          0     2      INTERFERON .ALPHA. (L) INTERFERON .ALPHA.-2C/CT
E11          0     2      INTERFERON .ALPHA. (L) INTERFERON .ALPHA.4/CT
E12          0     2      INTERFERON .ALPHA. (L) INTERFERON .ALPHA.8/CT
Relationship codes are not available in multifile sessions.

=> s e3
L1       14114 FILE MEDLINE       (2 TERMS)
L2           6 FILE CAPLUS
L3        1820 FILE BIOSIS
L4       17840 FILE EMBASE
L5           0 FILE WPIDS
L6       12576 FILE JICST-EPLUS

TOTAL FOR ALL FILES
L7       46356 INTERFERON/CT

=> e inflammatory response/ct 5
```

```
E#   FREQUENCY    AT     TERM
--   ---------    --     ----
E1           1          INFLAMMATORY RESPIRATORY DISORDER/CT
E2           1          INFLAMMATORY RESPIRATORY TRACT DISORDER/CT
E3         151      1 --> INFLAMMATORY RESPONSE/CT
E4           1          INFLAMMATORY RESPONSE ALTERATION/CT
E5           3          INFLAMMATORY RESPONSE AMPLIFICATION/CT

=> s e3+all
'"INFLAMMATORY RESPONSE"' NOT IN RELATIONSHIP FILE
RELATIONSHIP CODE 'ALL' IGNORED
L8           0 FILE MEDLINE       (1 TERM)
'"INFLAMMATORY RESPONSE"' NOT IN RELATIONSHIP FILE
RELATIONSHIP CODE '' IGNORED
L9           0 FILE CAPLUS        (1 TERM)
'"INFLAMMATORY RESPONSE"' NOT IN RELATIONSHIP FILE
RELATIONSHIP CODE 'ALL' IGNORED
L10        151 FILE BIOSIS        (1 TERM)
L11      45387 FILE EMBASE        (2 TERMS)
RELATIONSHIP 'ALL' IGNORED
RELATIONSHIPS DO NOT EXIST FOR FIELD 'CT'
L12          0 FILE WPIDS         (1 TERM)
'"INFLAMMATORY RESPONSE"' NOT IN RELATIONSHIP FILE
RELATIONSHIP CODE 'ALL' IGNORED
L13          0 FILE JICST-EPLUS   (1 TERM)

TOTAL FOR ALL FILES
L14      45538 E3+ALL

=> fil reg
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
FULL ESTIMATED COST                               8.90       9.70

FILE 'REGISTRY' ENTERED AT 14:45:03 ON 09 AUG 2001
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STRUCTURE FILE UPDATES:    8 AUG 2001  HIGHEST RN 350791-61-6
DICTIONARY FILE UPDATES:   8 AUG 2001  HIGHEST RN 350791-61-6

TSCA INFORMATION NOW CURRENT THROUGH January 11, 2001

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Structure search limits have been increased.  See HELP SLIMIT
for details.

=> s (trypsin or chemotrypsin or pepsin or collagenase)/cn
             1 TRYPSIN/CN
             0 CHEMOTRYPSIN/CN
             1 PEPSIN/CN
             1 COLLAGENASE/CN
```

```
L15          3 (TRYPSIN OR CHEMOTRYPSIN OR PEPSIN OR COLLAGENASE)/CN

=> s ?phospholipid?/cns
L16        333 ?PHOSPHOLIPID?/CNS

=> s ?phosphocholine?/cns
L17        196 ?PHOSPHOCHOLINE?/CNS

=> s (hexadecylphosphocholine or edelfosine)/cn
             1 HEXADECYLPHOSPHOCHOLINE/CN
             1 EDELFOSINE/CN
L18          2 (HEXADECYLPHOSPHOCHOLINE OR EDELFOSINE)/CN

=> s hydrochloric acid/cn;s sulfuric acid/cn;s sodium hydroxide/cn;s
potassium hydroxide/cn
L19          1 HYDROCHLORIC ACID/CN


L20          1 SULFURIC ACID/CN


L21          1 SODIUM HYDROXIDE/CN


L22          1 POTASSIUM HYDROXIDE/CN

=> e mcp 1/cn 5
E1           3     MCP/CN
E2           1     MCP (MAJOR CAPSID PROTEIN) (HUMAN PAPILLOMAVIRUS ISOLATE
GA1
                   15 GENE L1)/CN
E3           2 --> MCP 1/CN
E4           1     MCP 1 (PROTEIN)/CN
E5           1     MCP 1000/CN

=> s e3;e mcp 2/cn 5
L23          2 "MCP 1"/CN


E1           1     MCP 147B/CN
E2           1     MCP 150/CN
E3           1 --> MCP 2/CN
E4           1     MCP 200/CN
E5           1     MCP 239/CN

=> s e3;e mcp 3/cn 5
L24          1 "MCP 2"/CN


E1           1     MCP 239/CN
E2           1     MCP 2601/CN
E3           0 --> MCP 3/CN
E4           1     MCP 477/CN
E5           1     MCP 58/CN
```

```
=> e mcp 4/cn 5
E1            1     MCP 239/CN
E2            1     MCP 2601/CN
E3            0 --> MCP 4/CN
E4            1     MCP 477/CN
E5            1     MCP 58/CN

=> e rantes/cn 5
E1            1     RANTARIN/CN
E2            1     RANTEC D 1/CN
E3            0 --> RANTES/CN
E4            1     RANTES (CHEMOKINE) (1-CYSTEINE) (HUMAN)/CN
E5            1     RANTES (CHEMOKINE) (1-CYSTEINE,4-CYSTEINE) (HUMAN)/CN

=> s rantes/ct
'CT' IS NOT A VALID FIELD CODE
L25           0 RANTES/CT

=> s rantes?/cn;e "ip-10"/cn 5
L26          31 RANTES?/CN


E1            1     IP, ALUMINUM, COMPD. WITH URETIDINE/CN
E2            1     IP, ALUMINUM. COMPD. WITH N,N'-DIMETHYLETHYLENEDIAMINE/CN
E3            0 --> IP-10/CN
E4            1     IP-13650/CN
E5            1     IP-15770/CN

=> e mig/cn 5
E1            1     MIFOBATE/CN
E2            1     MIFORON/CN
E3            1 --> MIG/CN
E4            1     MIG 4A/CN
E5            1     MIG 4E/CN

=> s e3
L27           1 MIG/CN

=> fil medl,caplus,biosis,embase,wpids,jicst
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
FULL ESTIMATED COST                              63.90      73.60

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=> s (antigen? releas? agent? or (tumour or tumor)(w)debulk? or proteolytic
or trypsin or chymotrypsin or pepsin or collagenase or l15 or apoptosis
induc? or l16 or l17 or ?phospholipid? or ?phosphocholine?)
L28     190195 FILE MEDLINE
L29     275182 FILE CAPLUS
L30     216968 FILE BIOSIS
L31     169718 FILE EMBASE
LEFT TRUNCATION IGNORED FOR '?PHOSPHOLIPID?' FOR FILE 'WPIDS'
LEFT TRUNCATION IGNORED FOR '?PHOSPHOCHOLINE?' FOR FILE 'WPIDS'
L32      13025 FILE WPIDS
LEFT TRUNCATION IGNORED FOR '?PHOSPHOLIPID?' FOR FILE 'JICST-EPLUS'
LEFT TRUNCATION IGNORED FOR '?PHOSPHOCHOLINE?' FOR FILE 'JICST-EPLUS'
L33      20495 FILE JICST-EPLUS

TOTAL FOR ALL FILES
L34     885583 (ANTIGEN? RELEAS? AGENT? OR (TUMOUR OR TUMOR)(W) DEBULK? OR
               PROTEOLYTIC OR TRYPSIN OR CHYMOTRYPSIN OR PEPSIN OR
COLLAGENASE
               OR L15 OR APOPTOSIS INDUC? OR L16 OR L17 OR ?PHOSPHOLIPID? OR
               ?PHOSPHOCHOLINE?)
Left truncation is not valid in the specified search field in the
specified file.  The term has been searched without left truncation.
Examples: '?TERPEN?' would be searched as 'TERPEN?' and '?FLAVONOID'
would be searched as 'FLAVONOID.'

If you are searching in a field that uses implied proximity, and you
used a truncation symbol after a punctuation mark, the system may
interpret the truncation symbol as being at the beginning of a term.
Implied proximity is used in search fields indexed as single words,
for example, the Basic Index.

=> s (l34 or l18 or hexadecylphosphocholine or edelfosine) and (strong acid
or ((l19 or hydrochloric acid) and (l20 or sulfuric acid)) or ((l21 or sodium
hydroxide) and (l22 or potassium hydroxide)))
L35          21 FILE MEDLINE
L36         131 FILE CAPLUS
L37          35 FILE BIOSIS
L38          26 FILE EMBASE
L39          28 FILE WPIDS
L40           7 FILE JICST-EPLUS

TOTAL FOR ALL FILES
L41         248 (L34 OR L18 OR HEXADECYLPHOSPHOCHOLINE OR EDELFOSINE) AND
(STRON
               G ACID OR ((L19 OR HYDROCHLORIC ACID) AND (L20 OR SULFURIC
ACID)
               ) OR ((L21 OR SODIUM HYDROXIDE) AND (L22 OR POTASSIUM
HYDROXIDE)
```

))

=> s l41 and (l23 or l24 or l26 or l27 or (leucocyte or monocyte or t cell or granulocyte or eosinophil)(w)attract? or "mcp-1" or"mcp-2" or "mcp-3" or "mcp-4" or rantes or "ip-10" or mig or eotaxin or ifn or ir! or interferon or l14 or l7 ir inflam? response)
MISSING OPERATOR L7 IR
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> s l41 and (l23 or l24 or l26 or l27 or (leucocyte or monocyte or t cell or granulocyte or eosinophil)(w)attract? or "mcp-1" or"mcp-2" or "mcp-3" or "mcp-4" or rantes or "ip-10" or mig or eotaxin or ifn or ir! or interferon or l14 or l7 or inflam? response)
L42 1 FILE MEDLINE
L43 2 FILE CAPLUS
L44 0 FILE BIOSIS
L45 3 FILE EMBASE
L46 1 FILE WPIDS
L47 0 FILE JICST-EPLUS

TOTAL FOR ALL FILES
L48 7 L41 AND (L23 OR L24 OR L26 OR L27 OR (LEUCOCYTE OR MONOCYTE OR T CELL OR GRANULOCYTE OR EOSINOPHIL)(W) ATTRACT? OR "MCP-1" OR"MCP-2" OR "MCP-3" OR "MCP-4" OR RANTES OR "IP-10" OR MIG OR EOTAXIN OR IFN OR IR! OR INTERFERON OR L14 OR L7 OR INFLAM? RESPONSE)

=> dup rem l48
PROCESSING COMPLETED FOR L48
L49 6 DUP REM L48 (1 DUPLICATE REMOVED)

=> d cbib abs 1-6

L49 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2001 ACS
2001:136991 Document No. 134:198075 Triglyceride-free compositions and methods for enhanced absorption of hydrophilic therapeutic agents.
Patel, Mahesh V.; Chen, Feng-Jing (Lipocine, Inc., USA). PCT Int. Appl. WO 2001012155 A1 20010222, 113 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US18807 20000710. PRIORITY: US 1999-375636 19990817.
AB The present invention relates to triglyceride-free pharmaceutical compns., pharmaceutical systems, and methods for enhanced absorption of hydrophilic therapeutic agents. The compns. and systems include an absorption enhancing carrier, where the carrier is formed from a combination of at

least two surfactants, at least one of which is hydrophilic. A hydrophilic therapeutic agent can be incorporated into the compn., or can be co-administered with the compn. as part of a pharmaceutical system. The invention also provides methods of treatment with hydrophilic therapeutic agents using these compns. and systems. For example, when a compn. contg. Cremophor RH40 0.30, Arlacel 186 0.20, Na taurocholate 0.18, and propylene glycol 0.32 g, resp., was used, the relative absorption of PEG 4000 as a model macromol. drug was enhanced by 991%.

L49 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2001 ACS
2000:475560 Document No. 133:109949 Pharmaceutical compositions for treatment of diseased tissues. Lee, Clarence C.; Lee, Feng-Min (USA). PCT Int. Appl. WO 2000040269 A2 20000713, 26 pp. DESIGNATED STATES: W: AU, CA, CN, JP; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US191 20000105. PRIORITY: US 1999-PV114906 19990105.

AB A method to treat diseased tissue is provided where a cytotoxic compd. is administered to a patient in need of treatment in combination with an immunostimulant. Diseased cells and/or infectious microbes/viruses are killed by the cytotoxic compd. in the presence of the immunostimulant. The cell components including cellular contents and cell membrane fragments are presented by the immunostimulant to the host animal as antigens to stimulate the immune responses toward other diseased cells of the same type(s), that either remain in the vicinity or reside in distant tissues or organs. The cytotoxic mol. and immunostimulant are preferably applied locally at high concns., either sequentially or, preferably, simultaneously. For example, the compn. can be administered directly to a target cancer. The compn. can be prepd. in various forms, such as a paste, a time release molded solid shape, a soln., a mixt. with emulsifier, etc. Alternatively, the cytotoxic mol. and immunostimulant are applied in sequence.

L49 ANSWER 3 OF 6 MEDLINE DUPLICATE 1
96289841 Document Number: 96289841. PubMed ID: 8674897. The mechanism of collagen cross-linking in diabetes: a puzzle nearing resolution. Monnier V M; Glomb M; Elgawish A; Sell D R. (Institute of Pathology, School of Medicine, Case Western Reserve University, Cleveland, Ohio 44120, USA.. vmm3@po.cwru.edu) . DIABETES, (1996 Jul) 45 Suppl 3 S67-72. Ref: 106. Journal code: E8X; 0372763. ISSN: 0012-1797. Pub. country: United States. Language: English.

AB Considerable interest has been focused in recent years on the mechanism of collagen cross-linking by high glucose in vitro and in vivo. Experiments in both diabetic humans and in animals have shown that over time collagen becomes less soluble, less digestible by **collagenase**, more stable to heat-induced denaturation, and more glycated. In addition, collagen becomes more modified by advanced products of the Maillard reaction, i.e., immunoreactive advanced glycation end products and the glycoxidation markers carboxymethyllysine and pentosidine. Mechanistic studies have shown that collagen cross-linking in vitro can be uncoupled from glycation by the use of antioxidants and chelating agents. Experiments in the authors' laboratory revealed that approximately 50% of

carboxymethyllysine formed in vitro originates from pathways other than oxidation of Amadori products, i.e., most likely the oxidation of Schiff base-linked glucose. In addition, the increase in thermal stability of rat tail tendons exposed to high glucose in vitro or in vivo was found to strongly depend on H2O2 formation. The final missing piece of the puzzle is that of the structure of the major cross-link. We speculate that it is a nonfluorescent nonultraviolet active cross-link between two lysine residues, which includes a fragmentation product of glucose linked in a nonreducible bond labile to both **strong acids** and bases.

L49 ANSWER 4 OF 6 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1986-069825 [11] WPIDS
AB DE 3426049 A UPAB: 19930922
Prodn. of human tumour necrosis factor (I) comprises cultivating lymphoblastoid cells in a suitable medium with addition of a tumour-promoter (II). The extract, cell supernatant or filtrate is then treated with controlled-pore glass (CPG) and the adsorbed (I) then selectively eluted from the glass. The CPG-purificn. can be followed by purificn. on an anion-exchanger and/or a lectin column.

Also claimed are (1) (I), their salts and derivs., practically free of impurities; (2) mixts. of cleavage prods. formed by incubating (I) with **trypsin** or Staph. aureus V8 protease; (3) amino acid sequences contg. at least the gp. (A) and also DNA sequences coding for them.

NH2-Leu-Pro-Gly Val-Gly-Leu-X Pro-Ser-Ala-Ala Gln-X-Ala-(Arg or Tyr)-Glu-His-Pro -Lys-(Met or Val) Asp-Leu-Ala (A)

(X is an unidentified amino acid residue).

USE/ADVANTAGE - (I), and its fragments, have cytotoxic activity, so are useful in treatment of neoplastic disease. They also potentiate the activity of **interferon**. (I) can now be prepd. in sufficiently pure form for clinical testing. The CPG has high mechanical, chemical and thermal stability and can be reused many times after regeneration with **strong acid**.
0/11

L49 ANSWER 5 OF 6 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
79082528 EMBASE Document No.: 1979082528. Partial characterization of the age-related stabilizing factor of post-mature human collagen. I. By the use of bacterial **collagenase**. Hamlin C.R.; Luschin J.H.; Kohn R.R.. Inst. Pathol., Case West. Reserve Univ., Cleveland, Ohio 44106, United States. Experimental Gerontology 13/6 (403-414) 1978.
CODEN: EXGEAB. Pub. Country: United Kingdom. Language: English.
AB A stabilizing factor that causes resistance to digestion becomes increasingly important in collagen of post-mature individuals as they age.

This is demonstrated with paired diaphragm tendon and the dura mater from single individuals. The factor is rapidly and irreversibly lost when purified collagen is heated to 70.degree. C. Contact with 70% formic acid quickly abolished any detectable age differences, yet **strong acids** and bases did not disrupt the stabilizing factor. Treatment with cyanogen bromide in 70% formic acid at 30.degree. C failed to solubilize the collagen even when first heated to 100.degree. C in the presence of 0.01 M sodium hydroxide. Other treatments, including exposure

to sodium borohydride or glycosidases, had no detectable effect on the stabilizing factor. Increasing calcium concentration enhanced the rate of enzymatic digestion when using bacterial **collagenase**. Below 0.5 M calcium, age diffeences are readily observed with **collagenase**, but the differences are lost at higher concentrations. The age differences
are regained when the calcium ion concentration to reduced. This rapid reversal is in contrast ot the irreversible loss of the age difference caused by 70% formic acid traetment or collagen denaturants. These two latter treatments may not abolish the stabilization factor but could modify the collagen structure to the point where it can no longer retard the rate of **collagenase** digestion.

L49 ANSWER 6 OF 6 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
76155983 EMBASE Document No.: 1976155983. The blastic transformation of human
lymphocytes induced by streptococcal antigens. Mihalcu F.; Stefanescu M.; Platica C.. Lab. Streptococcal Meningococcal Infect., Inst. Cantacuzino, Bucharest, Romania. Archives Roumaines de Pathologie Experimentale et de Microbiologie 34/1-2 (121-128) 1975.
CODEN: APEMAR. Language: English.
AB A study was made of the normal human lymphocytes as induced by 5 streptococcal antigens: Streptolysin O (SO), M associated protein (MAP), streptokinase (SK), group A streptococcal carbohydrate (A-CHO) and group A
sonicated streptococcal cells. SO and MAP had a strong stimulating activity, the transformation rates depending on the antigen concentration,
the age of the lymphocyte donors, and the intensity of the (repeated) streptococcal contacts. SK, A-CHO and the streptococcal cells themselves did not induce blastic transformation. The streptococcal transforming factor was resistant to heat, to **proteolytic** enzymes and to **strong acids**. It is distinct from the hemolytic factor of the SO from which it may be separated. Maximal values of transformation
to SO were observed on the 4th and 5th day of lymphocyte cultivation.

```
=> s roussel e?/au,in
'IN' IS NOT A VALID FIELD CODE
L50          15 FILE MEDLINE
L51          32 FILE CAPLUS
L52          21 FILE BIOSIS
'IN' IS NOT A VALID FIELD CODE
L53          15 FILE EMBASE
L54          11 FILE WPIDS
L55           0 FILE JICST-EPLUS

TOTAL FOR ALL FILES
L56          94 ROUSSEL E?/AU,IN

=> s l56 and (134 or 118 or hexadecylphosphocholine or edelfosine or (tumour
or tumor)(w)(irl or inflam? response))
L57           1 FILE MEDLINE
L58           1 FILE CAPLUS
```

```
L59             1 FILE BIOSIS
L60             1 FILE EMBASE
L61             0 FILE WPIDS
L62             0 FILE JICST-EPLUS

TOTAL FOR ALL FILES
L63             4 L56 AND (L34 OR L18 OR HEXADECYLPHOSPHOCHOLINE OR EDELFOSINE
OR
                  (TUMOUR OR TUMOR)(W)(IR1 OR INFLAM? RESPONSE))

=> s l63 not l48
L64             1 FILE MEDLINE
L65             1 FILE CAPLUS
L66             1 FILE BIOSIS
L67             1 FILE EMBASE
L68             0 FILE WPIDS
L69             0 FILE JICST-EPLUS

TOTAL FOR ALL FILES
L70             4 L63 NOT L48

=> dup rem l70
PROCESSING COMPLETED FOR L70
L71              1 DUP REM L70 (3 DUPLICATES REMOVED)

=> d cbib abs

L71  ANSWER 1 OF 1     MEDLINE                              DUPLICATE 1
89093938  Document Number: 89093938.     PubMed ID: 2642945.    Identification
of
      a macrophage-activating factor in granules of the RNK large granular
      lymphocyte leukemia. Roussel E; Greenberg A H. (Department of
      Immunology, University of Manitoba, Winnipeg, Canada. ) JOURNAL OF
      IMMUNOLOGY, (1989 Jan 15) 142 (2) 543-8.  Journal code: IFB; 2985117R.
      ISSN: 0022-1767. Pub. country: United States. Language: English.
AB    Recent work from our laboratory has shown that NK cells rapidly release
      preformed factor(s) that stimulate monocyte oxidative metabolism and
      microbicidal activity. We have hypothesized that such factors could also
      activate macrophage (M phi) tumor lysis and might be stored in the
      cytoplasmic granules. Granules were isolated from the RNK large granular
      lymphocyte leukemias by nitrogen cavitation and Percoll fractionation of
      the cell homogenate. Utilizing CSF-1 differentiated murine bone
      marrow-derived M phi and P815 tumor target cells, a M phi-activating
      factor (MAF) was found. The MAF activity was identified in two peaks, the
      first was coincident with dense granule enzymes and was 60 times more
      concentrated per mg protein than a second peak in the cytosol fractions.
      Solubilization in 2 M NaCl was necessary to recover activity from both
      peaks. Granule NK-MAF required the simultaneous presence of LPS in order
      to induce tumoricidal activity. Kinetics of NK-MAF activation peaked
after
      12 h of exposure. The NK-MAF was short lived in the solubilized granules;
      however, its heat resistance allowed us to prepare enriched and stable
      preparations. Treatment of NK-MAF with pepsin but not
      trypsin completely abrogated its activity. The NK-MAF passed
      through an ultrafiltration membrane with a nominal cut-off of 10 kDa.
This
```

work indicates that NK cell granules contain a small heat-stable peptide capable of activating M phi tumoricidal activity.

=> s (l34 or l18 or hexadecylphosphocholine or edelfosine) and (tumour or tumor)(w)(ir1 or inflam? response)
L72 0 FILE MEDLINE
L73 0 FILE CAPLUS
L74 0 FILE BIOSIS
L75 0 FILE EMBASE
L76 0 FILE WPIDS
L77 0 FILE JICST-EPLUS

TOTAL FOR ALL FILES
L78 0 (L34 OR L18 OR HEXADECYLPHOSPHOCHOLINE OR EDELFOSINE) AND (TUMOU
R OR TUMOR)(W)(IR1 OR INFLAM? RESPONSE)

=> s l41 and (electrical current or electrode?)
L79 0 FILE MEDLINE
L80 1 FILE CAPLUS
L81 0 FILE BIOSIS
L82 0 FILE EMBASE
L83 0 FILE WPIDS
L84 0 FILE JICST-EPLUS

TOTAL FOR ALL FILES
L85 1 L41 AND (ELECTRICAL CURRENT OR ELECTRODE?)

=> d cbib abs hit

L85 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2001 ACS
1990:154841 Document No. 112:154841 Polyaniline-based enzyme **electrode**. Nakajima, Tadashi; Iino, Yasuhiro; Kawagoe, Takahiro (Bridgestone Corp., Japan). Eur. Pat. Appl. EP 300082 A2 19890125, 7 pp. DESIGNATED STATES: R: DE, FR, GB. (English). CODEN: EPXXDW. APPLICATION: EP 1987-112887 19870903. PRIORITY: JP 1987-184207 19870723.
AB An enzyme **electrode** comprises an enzyme immobilized on polyaniline (I) or a deriv., prepd. by electrolytic or chem. oxidative polymn. in an aq. acidic soln. contg. aniline or a deriv. Two stainless steel plates (2 mm .times. 20 mm .times. 250 .mu.m) were immersed as anode and cathode in an aq. soln. contg. aniline 5 and 42% HBF4 15 mL (50 mL total vol.), and I was formed by applying 50 mC of current at a const. current of 20 .mu.A. I was applied with redn. by cyclic voltammetry in Clark-Lubs 0.1 M H3PO4 buffer (pH 7.4) at a Ag/AgCl **electrode** potential of -200 to 500 mV with concomitant neutralization treatment (25.degree., 42 min). Glucose oxidase (500 units) was then immobilized on I with glutaraldehyde. In detn. of std. glucose concns. in serum, there was a linear correlation between current value and glucose concn. up to 500 mg glucose/L. The sensor was stable for 6 wks (200 measurements).
TI Polyaniline-based enzyme **electrode**
AB An enzyme **electrode** comprises an enzyme immobilized on polyaniline (I) or a deriv., prepd. by electrolytic or chem. oxidative

polymn. in an aq. acidic soln. contg. aniline or a deriv. Two stainless steel plates (2 mm .times. 20 mm .times. 250 .mu.m) were immersed as anode and cathode in an aq. soln. contg. aniline 5 and 42% HBF4 15 mL (50 mL total vol.), and I was formed by applying 50 mC of current at a const. current of 20 .mu.A. I was applied with redn. by cyclic voltammetry in Clark-Lubs 0.1 M H3PO4 buffer (pH 7.4) at a Ag/AgCl **electrode** potential of -200 to 500 mV with concomitant neutralization treatment (25.degree., 42 min). Glucose oxidase (500 units) was then immobilized on I with glutaraldehyde. In detn. of std. glucose concns. in serum, there was a linear correlation between current value and glucose concn. up to 500 mg glucose/L. The sensor was stable for 6 wks (200 measurements).

ST enzyme **electrode** polyaniline; glucose detn serum glucose oxidase polyaniline

IT Oxidizing agents
(in polymn. of aniline for enzyme **electrode** manuf.)

IT Electric current
(in polymn. of aniline for enzyme **electrode** prepn.)

IT Polymerization
(of aniline, electrolytic or chem., for enzyme **electrode** prepn.)

IT Immobilization, biochemical
(of enzymes, on polyaniline, for enzyme **electrodes**)

IT **Electrodes**
(bio-, enzyme, polyaniline-immobilized enzymes for)

IT 25233-30-1, Polyaniline 25233-30-1D, Polyaniline, derivs.
RL: ANST (Analytical study)
(enzyme immobilization on, for enzyme **electrodes**)

IT 64-19-7, Acetic acid, reactions 7601-90-3, Perchloric acid, reactions **7647-01-0, Hydrochloric acid**, reactions 7664-38-2, Phosphoric acid, reactions 7664-39-3, Hydrofluoric acid, reactions **7664-93-9, Sulfuric acid**, reactions 7697-37-2, Nitric acid, reactions 16872-11-0, Borofluoric acid
RL: ANST (Analytical study)
(in electrolytic or chem. polymn. of aniline for enzyme **electrode** prepn.)

IT 7705-08-0, Ferric chloride, reactions 7722-64-7, Potassium permanganate 7727-54-0, Ammonium persulfate 7778-50-9, Potassium dichromate
RL: RCT (Reactant)
(in oxidative polymn. of aniline for enzyme **electrode** manuf.)

IT 9001-05-2, Catalase 9001-36-9, Glucokinase 9001-37-0, Glucose oxidase 9001-60-9, Lactic acid dehydrogenase 9001-62-1, Lipase 9001-74-5, Penicillinase 9002-13-5, Urease 9003-99-0, Peroxidase **9013-93-8**, Phospholipase 9026-00-0, Cholesterol esterase 9028-79-9, Galactose oxidase 9031-72-5, Alcohol dehydrogenase 9032-08-0, Glucoamylase
RL: ANST (Analytical study)
(polyaniline-immobilized, enzyme **electrode** contg.)

IT 62-53-3, Aniline, reactions 62-53-3D, Aniline, derivs.
RL: RCT (Reactant)
(polymn. of, electrolytic or chem., for enzyme **electrode** manuf.)

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=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 08:46:48 ON 25 OCT 2001
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FILE LAST UPDATED: 24 Oct 2001  (20011024/ED)

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     FILE 'STNGUIDE' ENTERED AT 08:18:25 ON 25 OCT 2001

     FILE 'CAPLUS' ENTERED AT 08:31:44 ON 25 OCT 2001
L1         52294 S ANTIBOD? (L) MONOCLONAL?
L2          1434 S L1 (L) (IMMUNOTOXIN? OR CYTOTOX?)
L3        215773 S TUMOR# OR CARCINOMA? OR SARCOMA?
L4           504 S L3 AND L2
L5         50724 S ANTITUMOR (L) AGENT#
L6        111385 S (CANCER# OR TUMOR# OR NEOPLAS?) (L) INHIBIT?
L7        143642 S L5 OR L6
L8           365 S L7 AND L4
L9         97678 S LIPOLYTIC OR PROTEOLYTIC OR LIPASE# OR PROTEINASE# OR PROTEAS
L10              0 S L8 AND L9
L11              0 S L4 AND L0
L12              0 S L4 AND L9
L13             89 S L1 AND L3 AND L9
L14              0 S L2 AND L13
L15       164662 S PERMEAB? OR PERMEAB?/AB
L16              0 S L8 AND L15
L17              1 S L4 AND  L15
L18           1565 S L3 (L) DAMAG?
L19              2 S L18 AND L8
L20              1 S L8 AND FIBRIN#
L21             18 S L13 AND L5
L22            151 S L3 (L) FIBRIN#
L23              6 S L22 AND L1
L24              9 S L19 OR L20 OR  L23
L25             18 S L21 NOT  L24
```

FILE 'HCAPLUS' ENTERED AT 08:46:48 ON 25 OCT 2001

~~=> d .ca l24 1-19;d .ca l25 1-18~~
=> d .ca l24 1-19;d .ca l25 1-18

L24 ANSWER 1 OF 9 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:586195 CAPLUS
DOCUMENT NUMBER: 132:92063
TITLE: Suppression of solid tumor growth by a **monoclonal antibody** against tumor vasculature in rats: involvement of intravascular thrombosis and fibrinogenesis
AUTHOR(S): Ohizumi, Iwao; Taniguchi, Kenji; Saito, Hiroyuki; Kawata, Hiromitsu; Tsunoda, Shin-Ichi; Makimoto, Hiroo; Wakai, Yukiko; Tsutsumi, Yasuo; Nakagawa, Shinsaku; Utoguchi, Naoki; Kaiho, Shin-Ichi; Ohsugi, Yoshiyuki; Mayumi, Tadanori
CORPORATE SOURCE: Fuji Gotemba Research Laboratories, Chugai Pharmaceutical Co. Ltd., Shizuoka, 412-8513, Japan
SOURCE: Int. J. Cancer (1999), 82(6), 853-859
CODEN: IJCNAW; ISSN: 0020-7136
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We have reported that immunization of rat tumor-derived endothelial cells (TEC) isolated from KMT-17 solid tumors results in the generation of several monoclonal antibodies (MAbs). TES-23, one of these MAbs, recognizes a naturally occurring 80-kDa antigen expressed on endothelial cells of tumor blood vessels. To det. whether such MAbs can suppress solid tumor growth in vivo by impairment of endothelial cells in tumors following direct binding, we tested the biodistribution of 125I-labeled TES-23 in rats bearing KMT-17 solid tumors. We also examd. the effect of treatment using unconjugated TES-23 on tumor growth and histo-pathol. changes in tumor tissues. Biodistribution studies showed localization of TES-23 into tumor tissues 60 min after i.v. injection. TES-23 suppressed significantly the growth of KMT-17 solid tumors following administration for 5 days. Histo-pathol. examn. showed that TES-23 caused degeneration, apoptosis and/or necrosis and denudation of endothelial cells in viable tumor areas following local aggregation and adhesion of lymphocytes, with subsequent intravascular thrombus formation by platelets and fibrin. Our results indicate that TES-23, which recognizes TEC, can target endothelial cells of solid tumor vasculature directly, resulting in growth suppression in vivo by redn. of blood flow due to intravascular thrombosis. Our results also suggest that targeting tumor vasculature is a potentially attractive approach for the treatment of solid tumors.
CC 15-3 (Immunochemistry)
ST tumor suppression **monoclonal antibody** vascular endothelium
IT Blood vessel
(endothelium; suppression of solid tumor growth by a **monoclonal antibody** against tumor vasculature in rats in relation to intravascular thrombosis and fibrinogenesis)
IT **Antibodies**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**monoclonal**, TES-23; suppression of solid tumor growth by a **monoclonal antibody** against tumor vasculature in rats in relation to intravascular thrombosis and fibrinogenesis)
IT Antigens
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(suppression of solid tumor growth by a **monoclonal antibody** against tumor vasculature antigen in rats in relation to intravascular thrombosis and fibrinogenesis)

IT Antitumor agents
Thrombosis
(suppression of solid tumor growth by a **monoclonal antibody** against tumor vasculature in rats in relation to intravascular thrombosis and fibrinogenesis)
IT **Fibrins**
RL: MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(suppression of solid **tumor** growth by a **monoclonal antibody** against **tumor** vasculature in rats in relation to intravascular thrombosis and fibrinogenesis)
REFERENCE COUNT: 20
REFERENCE(S): (1) Boehm, T; Nature (Lond) 1997, V390, P404 CAPLUS
(2) Brooks, P; Science 1994, V264, P569 CAPLUS
(3) Burrows, F; Clin Cancer Res 1995, V1, P1623 CAPLUS
(4) Denny, W; J Pharm Pharmacol 1998, V50, P387 CAPLUS
(6) Ebina, T; Cancer Res 1977, V37, P4423 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 2 OF 9 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:141866 CAPLUS
DOCUMENT NUMBER: 131:310
TITLE: A Fas-dependent component in 5-fluorouracil/leucovorin-induced cytotoxicity in colon **carcinoma** cells
AUTHOR(S): Tillman, David M.; Petak, Istvan; Houghton, Janet A.
CORPORATE SOURCE: Department of Molecular Pharmacology, St. Jude Children's Research Hospital, Memphis, TN, 38105, USA
SOURCE: Clin. Cancer Res. (1999), 5(2), 425-430
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We have shown previously that thymineless death in thymidylate synthase-deficient (TS-) colon carcinoma cells is mediated via Fas/FasL interactions after deoxythymidine (dThd) deprivation, and that Fas-dependent sensitivity of human colon carcinoma cell lines may be dependent upon the level of Fas expressed. The objective of this study was to elucidate whether a Fas-dependent component exists in 5-fluorouracil (FUra)/leucovorin (LV)-induced cytotoxicity of colon carcinoma cells, and whether this may be potentiated by IFN-.gamma.-induced elevation in Fas expression, using the HT29 cell line as a model. The cytotoxic activity of FUra/LV was inhibited by dThd in HT29 cells and also, in part, by NOK-1+NOK-2 MoAbs that prevent Fas/FasL interactions. FUra/LV-induced cytotoxicity was significantly potentiated by IFN-.gamma., reversed by exposure to NOK-1+NOK-2 antibodies, and correlated with a 4-fold induction of Fas expression in the presence of IFN-.gamma. and significant elevation in expression of FasL. Using five addnl. human colon carcinoma cell lines, FUra/LV-induced cytotoxicity was dThd-dependent in GC3/c1, VRC5/c1, and Caco2 but not in HCT8 or HCT116 cells. Like HT29 cells, this cytotoxicity was potentiated by IFN-.gamma. in GC3/c1 and VRC5/c1 but not in Caco2, which fails to express Fas, nor in HCT8 and HCT116, in which no dThd-dependent FUra-induced cytotoxicity was demonstrated. Data suggest that a Fas-dependent component, potentiated by IFN-.gamma., exists in FUra/LV-induced cytotoxicity but requires FUra/LV-induced DNA damage for IFN-.gamma.-induced potentiation to occur.
CC 1-6 (Pharmacology)
ST Fas fluorouracil leucovorin colon **carcinoma**
IT Fas antigen
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Fas-dependent component in 5-fluorouracil/leucovorin-induced cytotoxicity in colon **carcinoma**)
IT **Antitumor agents**

(colon **carcinoma**; Fas-dependent component in 5-fluorouracil/leucovorin-induced cytotoxicity in colon **carcinoma**)

IT Intestine, **neoplasm**
(colon, **carcinoma**, **inhibitors**; Fas-dependent component in 5-fluorouracil/leucovorin-induced cytotoxicity in colon **carcinoma**)

IT DNA
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**damage**; Fas-dependent component in 5-fluorouracil/leucovorin-induced cytotoxicity in colon **carcinoma**)

IT **Antibodies**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**monoclonal**, NOK-1+NOK-2; Fas-dependent component in 5-fluorouracil/leucovorin-induced **cytotoxicity** in colon **carcinoma**)

IT Interferons
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(.gamma.; Fas-dependent component in 5-fluorouracil/leucovorin-induced cytotoxicity in colon **carcinoma**)

IT 51-21-8, 5-Fluorouracil 58-05-9, Leucovorin
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Fas-dependent component in 5-fluorouracil/leucovorin-induced cytotoxicity in colon **carcinoma**)

IT 50-89-5, Thymidine, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Fas-dependent component in 5-fluorouracil/leucovorin-induced cytotoxicity in colon **carcinoma**)

REFERENCE COUNT: 25

REFERENCE(S):
(1) Benz, C; Cancer Res 1981, V41, P994 CAPLUS
(2) Branca, A; Nature 1981, V294, P768 CAPLUS
(3) Brunda, M; Int J Cancer 1986, V37, P287 CAPLUS
(4) Cheshire, J; Mol Cell Biol 1997, V17, P6746 CAPLUS
(5) Chu, E; Mol Pharmacol 1993, V43, P527 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 3 OF 9 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1997:540352 CAPLUS
DOCUMENT NUMBER: 127:134687
TITLE: Tumor necrosis factor binding ligands
INVENTOR(S): Rathjen, Deborah Ann; Aston, Roger
PATENT ASSIGNEE(S): Peptide Technology Ltd., Australia
SOURCE: U.S., 43 pp. Cont.-in-part of U.S. Ser. No. 828,956, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5644034	A	19970701	US 1994-344133	19941123
WO 9102078	A1	19910221	WO 1990-AU337	19900807
W: AU, CA, JP, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, IT, LU, NL, SE				
US 5959087	A	19990928	US 1997-823893	19970317
US 2001018507	A1	20010830	US 2000-736792	20001213
US 2001018508	A1	20010830	US 2000-737121	20001213
US 2001023287	A1	20010920	US 2000-736793	20001213

PRIORITY APPLN. INFO.: AU 1989-5662 A 19890807
AU 1989-7576 A 19891124

WO 1990-AU337	A	19900807
US 1992-828956	B2	19920218
WO 1990-AU377	W	19900807
US 1994-344133	A1	19941123
US 1997-823893	A1	19970317
US 1999-364039	A1	19990730

AB The present invention relates to ligands which bind to human tumor necrosis factor alpha (TNF) in a manner such that upon binding of these ligands to TNF the biol. activity of TNF is modified. In preferred forms the ligand binds to TNF in a manner such that the induction of endothelial procoagulant activity of the TNF is inhibited; the binding of TNF to receptors on endothelial cells is inhibited; the induction of fibrin deposition in the tumor and tumor regression activities of the TNF are enhanced; and the cytotoxicity and receptor binding activities of the TNF are unaffected or enhanced on tumor cells. The ligand is preferably an antibody, F(ab) fragment, single domain antibody (dABs) single chain antibody or a serum binding protein. It is preferred, however, that the ligand is a monoclonal antibody or F(ab) fragment thereof.

IC ICM C07K016-24
ICS C12N005-12

NCL 530388230

CC 15-3 (Immunochemistry)

ST **monoclonal antibody** tumor necrosis factor alpha; antitumor TNFa epitope **monoclonal antibody** fragment

IT **Fibrins**
RL: BOC (Biological occurrence); BIOL (Biological study); OCCU (Occurrence)
(deposition in **tumor**; **tumor** necrosis factor binding ligands or antibody fragments for enhancing antitumor activity of TNF.alpha.)

IT **Tumors** (animal)
(**fibrin** deposition; **tumor** necrosis factor binding ligands or antibody fragments for enhancing antitumor activity of TNF.alpha.)

IT **Monoclonal antibodies**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tumor necrosis factor binding ligands or **antibody** fragments for enhancing antitumor activity of TNF.alpha.)

L24 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER:	1992:400904 CAPLUS
DOCUMENT NUMBER:	117:904
TITLE:	Method of treating viral infection with anti-tumor necrosis factor (TNF) ligand
INVENTOR(S):	Rathjen, Deborah Ann; Aston, Roger; Ramshaw, Ian Alastair
PATENT ASSIGNEE(S):	Peptide Technology Ltd., Australia
SOURCE:	PCT Int. Appl., 64 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9203145	A1	19920305	WO 1991-AU400	19910827
W: AU, CA, JP, US RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE				
AU 9184248	A1	19920317	AU 1991-84248	19910827
AU 654501	B2	19941110		
JP 06500323	T2	19940113	JP 1991-514178	19910827
EP 608212	A1	19940803	EP 1991-915297	19910827

R: CH, DE, DK, FR, GB, IT, LI, SE
PRIORITY APPLN. INFO.: AU 1990-1976 19900827
WO 1991-AU400 19910827

AB Virus infection in a mammal is treated by administering an anti-TNF ligand either alone or in combination with TNF. The ligand is such that when it binds to TNF, the induction of endothelial procoagulant activity by the TNF is inhibited and the antiviral activity of the TNF is unaffected or enhanced. A compn. for use in treating viral infections in a mammal is also provided. Monoclonal antibodies (MAbs) to TNF were prepd. and tested for effect on TNF bioactivity. Regions on human TNF recognized by the MAbs were identified using overlapping synthetic peptides of human TNF. MAb 32, which potentiates the in vivo tumor regression and antiviral activity of TNF, bound to TNF residues 1-26, 117-128, and 141-153. Mice treated with human TNF-.alpha.-MAb 32 complex 24 h prior to infection with vaccinia virus showed reduced virus levels in ovaries, lungs, and spleen compared to mice treated with TNF alone.

IC ICM A61K037-02
ICS A61K039-395; A61K037-66

CC 1-5 (Pharmacology)
Section cross-reference(s): 15, 63

ST antiviral tumor necrosis factor antiligand; **monoclonal antibody** TNF complex antiviral

IT Neoplasm, metabolism
(**fibrin** deposition, induction of, with **tumor** necrosis factor, antiligand effect on)

IT **Fibrins**
RL: PEP (Physical, engineering or chemical process); PROC (Process)
(**tumor** deposition of, induction of, with **tumor** necrosis factor, antiligand effect on)

IT Carcinoma
(tumor necrosis factor receptors on, of human, tumor necrosis factor binding to, **monoclonal antibody** 32 potentiation of)

IT **Antibodies**
RL: BIOL (Biological study)
(**monoclonal**, to tumor necrosis factor, for treatment of viral infection in mammal)

IT Lymphokines and Cytokines
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(tumor necrosis factor-.alpha., complexes with **monoclonal antibody** 32 to tumor necrosis factor of human, antiviral activity of)

IT Virus, animal
(vaccinia, mouse infection with, tumor necrosis factor-**monoclonal antibody** complex inhibition of)

IT 136040-07-8 136040-08-9 136040-09-0 136040-10-3 136040-11-4
136040-12-5 136040-13-6 136040-14-7 136040-15-8 136040-16-9
RL: BIOL (Biological study)
(**monoclonal antibodies** to tumor necrosis factor response to)

L24 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1991:549906 CAPLUS
DOCUMENT NUMBER: 115:149906
TITLE: Glucose oxidase conjugated with anti-endothelial monoclonal antibodies: in vitro and in vivo studies
AUTHOR(S): Muzykantov, V. R.; Danilov, S. M.
CORPORATE SOURCE: Inst. Exp. Cardiol., Moscow, USSR
SOURCE: Int. J. Radiat. Biol. (1991), 60(1-2), 11-15
CODEN: IJRBE7; ISSN: 0955-3002
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To study the cytodestructive potential of glucose oxidase (GO)-antibody,

various antibodies were used to endothelial cells (EC) and to their extracellular matrix. EC are of great interest as a target for selective elimination (e.g. tumor endothelium). The data show that antibody-GO bring about specific targeting and selective/local destructive effects both in vitro and in vivo. Both intra- and extracellular modes of action were obsd., the former being more efficient.

CC 1-6 (Pharmacology)

ST glucose oxidase **monoclonal antibody** antitumor; **immunotoxin** glucose oxidase antitumor

IT **Neoplasm inhibitors**
(glucose oxidase conjugated with anti-endothelial monoclonal antibodies, toxicity to blood vessel endothelium of humans in)

IT Extracellular matrix
(proteins of, glucose oxidase-antibody conjugate to, toxicity to human vascular endothelium of, **tumor inhibition** in relation to)

IT Collagens, compounds
Fibronectins
RL: BIOL (Biological study)
(conjugates, with glucose oxidase-antibody, toxicity to human vascular endothelium of, **tumor inhibition** in relation to)

IT Blood vessel, toxic chemical and physical **damage**
(endothelium, glucose oxidase-antibody conjugate toxicity to human, **tumor inhibition** in relation to)

IT Toxins
RL: BIOL (Biological study)
(immuno-, glucose oxidase-contg., characterization of, **neoplasm inhibition**, in relation to)

IT Antibodies
RL: BIOL (Biological study)
(monoclonal, glucose oxidase conjugates, to extracellular matrix proteins and human vascular endothelium, toxicity of, **tumor inhibition** in relation to)

IT 9001-37-0D, Glucose oxidase, monoclonal antibody conjugates
RL: BIOL (Biological study)
(to extracellular matrix proteins and human vascular endothelium, toxicity of, **tumor inhibition** in relation to)

L24 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1991:534002 CAPLUS
DOCUMENT NUMBER: 115:134002
TITLE: Tumor necrosis factor .alpha. (TNF) binding ligands for selective inhibition and enhancement of TNF activities
INVENTOR(S): Rathjen, Deborah Anne; Aston, Roger
PATENT ASSIGNEE(S): Peptide Technology Ltd., Australia
SOURCE: PCT Int. Appl., 83 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9102078	A1	19910221	WO 1990-AU337	19900807
W: AU, CA, JP, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, IT, LU, NL, SE				
CA 2064915	AA	19910208	CA 1990-2064915	19900807
AU 9061454	A1	19910311	AU 1990-61454	19900807
AU 640400	B2	19930826		
EP 486526	A1	19920527	EP 1990-911467	19900807
EP 486526	B1	19960522		

EP 486526	B2	20010307			
R: CH, DE, DK, ES, FR, GB, IT, LI, NL, SE					
JP 04507195	T2	19921217	JP 1990-510780		19900807
US 5644034	A	19970701	US 1994-344133		19941123
US 2001018507	A1	20010830	US 2000-736792		20001213
US 2001018508	A1	20010830	US 2000-737121		20001213
PRIORITY APPLN. INFO.:			AU 1989-5662	A	19890807
			AU 1989-7576	A	19891124
			WO 1990-AU337	A	19900807
			US 1992-828956	B2	19920218
			US 1994-344133	A1	19941123
			US 1997-823893	A1	19970317
			US 1999-364039	A1	19990730

AB Monoclonal antibodies (MAbs) active against human TNF have been characterized with respect to their effects on the antitumor effect of TNF (both in vitro and in vivo), TNF receptor binding, activation of coagulation, and their topog. specificities have been defined. Different topog. regions of TNF are shown to be assocd. with different activities. Therefore, antibodies or ligands have been identified which selectively enhance or inhibit TNF .alpha. activity, thereby providing for improved therapeutic agents and regimes including TNF .alpha.. MAbs 1, 47, and 54, binding a epitope on human TNF, inhibited cytotoxicity, tumor regression, induction of endothelial procoagulant, tumor fibrin deposition, and receptor binding activities of TNF and, thus, would be useful for treating toxic shock and other conditions of bacterial, viral, and parasitic infection where TNF levels are high requiring complete neutralization of TNF. Other MAbs, e.g. MAb 32, are more appropriate as agents for coadministration with TNF during cancer therapy since they inhibit coagulation activation and enhance tumor regression activity of TNF. MAb 32 bound all the loop regions assocd. with residues 1-26, 117-128, and 141-153 of TNF.

IC ICM C12P021-08
ICS C07K015-28

CC 15-5 (Immunochemistry)
Section cross-reference(s): 1

ST tumor necrosis factor binding ligand; **monoclonal antibody** TNF activity modification

IT Parasite
Virus
(infection with, tumor necrosis factor levels high in, **monoclonal antibodies** inhibiting TNF in treatment of)

IT **Fibrins**
RL: PEP (Physical, engineering or chemical process); PROC (Process)
(**tumor** deposition of, induction of, by **tumor** necrosis factor .alpha. of human, ligand modification of)

IT Infection
(tumor necrosis factor levels high in, **monoclonal antibodies** inhibiting TNF in treatment of)

IT **Antibodies**
RL: BIOL (Biological study)
(**monoclonal**, to tumor necrosis factor .alpha. of human, TNF activity modification with)

L24 ANSWER 7 OF 9 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER:	1989:420216 CAPLUS
DOCUMENT NUMBER:	111:20216
TITLE:	Affinity enhancement immunological reagents for detection and killing of specific target cells
INVENTOR(S):	Barbet, Jacques; Delaage, Michel; Le Doussal, Jean Marc
PATENT ASSIGNEE(S):	Immunotech S. A., Fr.
SOURCE:	Eur. Pat. Appl., 13 pp. CODEN: EPXXDW

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 263046	A1	19880406	EP 1987-430031	19870916
EP 263046	B1	19920415		
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
FR 2604092	A1	19880325	FR 1986-13146	19860919
FR 2604092	B1	19900413		
US 5256395	A	19931026	US 1987-96829	19870910
AT 74769	E	19920515	AT 1987-430031	19870916
ES 2032468	T3	19930216	ES 1987-430031	19870916
CA 1306414	A1	19920818	CA 1987-547184	19870917
AU 8778656	A1	19880421	AU 1987-78656	19870918
AU 613318	B2	19910801		
JP 63159327	A2	19880702	JP 1987-234680	19870918
JP 2612454	B2	19970521		

PRIORITY APPLN. INFO.: FR 1986-13146 19860919
EP 1987-430031 19870916

AB Immunol. reagents comprise (a) a monoclonal antibody or fragment, with binding affinity for a desired antigen (e.g. cell-, tumor-, or tissue-assocd.), conjugated to a monoclonal antibody or fragment with binding affinity for a desired hapten; and (b) a synthetic mol. comprising .gtoreq.2 haptens (which bind the conjugate), .gtoreq.1 site suitable for radiolabeling, labeling with a stable paramagnetic metal, or coupling to a drug or toxin, and a chem. structure to link these functions. These reagents can bind to target cells in a specific way; the hapten localizes preferentially on the antigen-bearing cells even in the presence of excess antibody conjugates (affinity enhancement). The reagents are used in vitro or in vivo to detect tumors, metastases, or other tissue injuries when the synthetic mol. carries radioactive or paramagnetic compds., and to kill target cells when carrying radioactive compds., drugs, or toxins. The F(ab')2 fragment of anti-Lyb8.2 antibody (clone CY34) was treated with succinimidyl 4-(N-maleimidomethyl)cyclohexane-1-carboxylate and conjugated to the Fab' fragment of anti-2,4-DNP antibody. BALB/c mouse spleen cells (107 cells/mL), contg. Lyb8.2 antigens, were incubated with the conjugate (3.10 .times. 10-9M) for 2 h at 37.degree. before binding 111In-labeled bis[N.epsilon.-(2,4-dinitrophenyl)-L-lysyl]diethylenetriaminepentaacetic acid (I) or [N.epsilon.-(2,4-dinitrophenyl)-L-lysyl]diethylenetriaminepentaacetic acid (II) (both prepd. from 2,4-dinitrophenyllysine and DTPA cyclic anhydride). Under these conditions, 26% (bound/free) of labeled I became bound to the cells (of which .apprx.70% are Lyb8.2 pos.), as opposed to only 6% (bound/free) of the monomeric tracer II. In the absence of conjugate, the nonspecific binding of labeled tracers was .apprx.0.2%.

IC ICM A61K049-00
ICS A61K043-00; A61K047-00

CC 8-9 (Radiation Biochemistry)
Section cross-reference(s): 34

ST monoclonal antibody specificity hapten cell antigen; immunoreagent diagnosis **neoplasm inhibition**

IT **Cytotoxic** agents
Neoplasm inhibitors
(dual-specificity **monoclonal antibodies** and hapten-toxin conjugates as)

IT Antigens
Fibrins
Myosins
RL: BIOL (Biological study)
(dual-specificity monoclonal antibodies to hapten and, for detecting

and killing target cells)
IT Antigens
RL: BIOL (Biological study)
(**tumor**-assocd., dual-specificity monoclonal antibodies to hapten and, for detecting and killing target cells)

L24 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1988:622473 CAPLUS
DOCUMENT NUMBER: 109:222473
TITLE: Fibrinolytic composition containing fibrinolytic enzymes and surface-active ethylene oxide-propylene oxide copolymers
INVENTOR(S): Hunter, Robert L.; Duncan, Alexander
PATENT ASSIGNEE(S): Emory University, USA
SOURCE: PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 8706836	A1	19871119	WO 1987-US1067	19870508
W: AU, BB, BG, BR, DK, FI, HU, JP, KP, KR, LK, MC, MG, MW, NO, RO, SD, SU				
RW: AT, BE, BJ, CF, CG, CH, CM, DE, FR, GA, GB, IT, LU, ML, MR, NL, SE, SN, TD, TG				
US 4801452	A	19890131	US 1987-45459	19870507
AU 8774840	A1	19871201	AU 1987-74840	19870508
AU 599392	B2	19900719		
BR 8707308	A	19880913	BR 1987-7308	19870508
JP 01500592	T2	19890301	JP 1987-503333	19870508
JP 06010139	B4	19940209		
HU 47431	A2	19890328	HU 1987-3138	19870508
EP 451880	A2	19911016	EP 1991-108946	19870508
EP 451880	A3	19911227		
R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
AT 102045	E	19940315	AT 1987-903587	19870508
AT 142502	E	19960915	AT 1992-106213	19870508
CA 1297792	A1	19920324	CA 1987-537052	19870513
IL 82519	A1	19920525	IL 1987-82519	19870514
IN 165476	A	19891028	IN 1987-CA393	19870518
US 4873083	A	19891010	US 1987-136034	19871221
FI 8800163	A	19880114	FI 1988-163	19880114
FI 94928	B	19950815		
FI 94928	C	19951127		
NO 8800141	A	19880314	NO 1988-141	19880114
ES 2009264	A6	19890916	ES 1988-1268	19880426
US 4997644	A	19910305	US 1990-518348	19900503
US 5017370	A	19910521	US 1990-518510	19900503
US 5030448	A	19910709	US 1990-519148	19900504
US 5032394	A	19910716	US 1990-518776	19900504
US 5039520	A	19910813	US 1990-520371	19900504
US 5041288	A	19910820	US 1990-519005	19900504
US 5071649	A	19911210	US 1990-519161	19900504
US 5028599	A	19910702	US 1990-522168	19900511
US 5078995	A	19920107	US 1990-522206	19900511
US 5089260	A	19920218	US 1990-522193	19900511
US 5080894	A	19920114	US 1990-525111	19900517
US 5064643	A	19911112	US 1990-560010	19900725
US 5198211	A	19930330	US 1991-802331	19911204
US 5240701	A	19930831	US 1992-827640	19920129

NO 9202262	A	19880314	NO 1992-2262	19920609
JP 06016567	A2	19940125	JP 1992-272491	19920917
JP 06016571	A2	19940125	JP 1992-272493	19920917
JP 06053685	B4	19940720		
JP 06016562	A2	19940125	JP 1992-272494	19920917
JP 07035337	B4	19950419		
JP 06016565	A2	19940125	JP 1992-272497	19920917
JP 06024993	A2	19940201	JP 1992-272496	19920917
JP 07035336	B4	19950419		
JP 06040924	A2	19940215	JP 1992-272492	19920917
JP 07035338	B4	19950419		
JP 06048951	A2	19940222	JP 1992-272495	19920917
JP 06100454	A2	19940412	JP 1992-272490	19920917
JP 07057730	B4	19950621		
US 5250294	A	19931005	US 1992-977530	19921117
US 5240702	A	19930831	US 1992-985746	19921204
US 5648071	A	19970715	US 1995-409549	19950324

PRIORITY APPLN. INFO.:

US 1986-863582	19860515
US 1987-43088	19870429
US 1987-43888	19870429
US 1987-45459	19870507
EP 1987-903587	19870508
WO 1987-US1067	19870508
US 1987-136034	19871221
NO 1988-141	19880114
US 1988-222874	19880721
US 1988-226359	19880729
US 1989-303791	19890130
US 1989-392224	19890810
US 1989-403017	19890905
US 1989-457918	19891227
US 1990-522206	19900511
US 1991-802331	19911204
US 1992-827639	19920129
US 1992-881203	19920511
US 1993-131865	19931005
US 1994-259147	19940613

AB Compns. which dissolve blood clots and reestablish and maintain blood flow through thrombosed coronary or other blood vessels contain a fibrinolytic enzyme such as streptokinase, urokinase, or tissue plasminogen activator, and the surface-active block copolymer HO(C2H4O)b(C3H6O)a(C2H4O)bH [I; (C3H6O)a group has a mol. wt. 950-4000; the (C2H4O) groups comprise 50-90% of the wt. of the polymer.]. Isolated rat hearts were perfused with nonheparinized washed whole human blood, the blood flow was completely stopped for 30 min, and the hearts were reperfused for 10 min with nonheparinized washed whole human blood to which I and/or streptokinase were added. I and streptokinase were about equally effective in protecting the hearts; the I-streptokinase combination was clearly more effective than either I or streptokinase. A formulation for an 180 lb patient with pulmonary embolism is: urokinase 500 mg, 0.9% NaCl 90 mL, I (total mol. wt. .apprx.8400, the (C3H3O)a segment weighs .apprx.1750) 6 g, and water to 195 mL. A priming dose of this formulation would be delivered at 90 mL/h for 10 min, followed by continuous infusion at 15 mL/h for 12 h.

IC ICM A61K037-54
ICS A61K037-547; A61K031-725

CC 1-8 (Pharmacology)
Section cross-reference(s): 63

IT **Fibrins**
RL: REM (Removal or disposal); PROC (Process)
(removal of, from **tumors**, fibrinolytic compn. contg. surface-active copolymer for)

IT **Antibodies**

RL: BIOL (Biological study)
(**monoclonal**, tumor-specific, for tumor diagnosis, blood flow improvement in relation to)

L24 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1987:420272 CAPLUS
DOCUMENT NUMBER: 107:20272
TITLE: Determination of fibrin and fibrin(ogen) derivatives by **monoclonal antibodies**: a double blind comparative study
AUTHOR(S): Creighton, L. C.; Gaffney, P. J.; Graeff, H.; Hafter, R.; Mueller-Berghaus, G.; Nieuwenhuizen, W.; Scheefers-Borchel, U.
CORPORATE SOURCE: Clin. Res. Unit Blood Coagulation Thrombosis, Max-Planck-Ges., Giessen, D-6300, Fed. Rep. Ger.
SOURCE: Int. Congr. Ser. - Excerpta Med. (1986), 722(Fibrinogen Its Deriv.), 257-60
CODEN: EXMDA4; ISSN: 0531-5131
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The detn. of fibrin and fibrinogen degrdn. products in patient plasma samples was examd. using the sol. fibrin assay, the X-oligomer assay, the D-dimer test, and the total degrdn. products assay. Low levels of derivs. were found in control samples and elevated levels in the clin. samples. A good correlation of assay results were obtained between the D-dimer, total degrdn. products, and X-oligomer assays. The correlations between sol. fibrin and D-dimer and total degrdn. products assays were weaker.
CC 9-10 (Biochemical Methods)
Section cross-reference(s): 15
ST fibrin degrdn product detn plasma; immunoassay **monoclonal antibody** fibrinogen
IT Fibrinogen degradation products
RL: ANT (Analyte); ANST (Analytical study)
(detn. of, in blood plasma by **monoclonal antibodies**, immunoassays comparison for)
IT Blood analysis
(fibrin and fibrinogen degrdn. products detn. in, of human by **monoclonal antibodies**, immunoassays comparison for)
IT **Sarcoma**
(**fibrin** and fibrinogen degrdn. products of human blood plasma in, of uterus)
IT Immunochemical analysis
(immunoassay, for fibrin and fibrinogen degrdn. products, in human blood plasma using **monoclonal antibodies**, comparison of)
IT **Antibodies**
RL: ANST (Analytical study)
(**monoclonal**, in fibrin and fibrinogen degrdn. products detn. in human blood plasma by immunoassays)
IT Uterus, neoplasm
(**sarcoma**, **fibrin** and fibrinogen degrdn. products of human blood plasma in)

L25 ANSWER 1 OF 18 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:582030 CAPLUS
DOCUMENT NUMBER: 135:177279
TITLE: cDNA encoding human transmembrane serine **proteases**
INVENTOR(S): Madison, Edwin L.; Ong, Edgar O.; Yeh, Jiunn-Chern
PATENT ASSIGNEE(S): Corvas International, Inc., USA

SOURCE: PCT Int. Appl., 256 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001057194	A2	20010809	WO 2001-US3471	20010202

W: AE, AG, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:
US 2000-179982 P 20000203
US 2000-183542 P 20000218
US 2000-213124 P 20000622
US 2000-220970 P 20000726
US 2000-657986 A2 20000908
US 2000-234840 P 20000922

AB The invention provided 6 human polypeptides that include the protease domain of a type II transmembrane serine protease (MTSP) as a single chain. MTSP are differentially expressed in tumor and non-tumor cells. Methods using the polypeptides to identify compds. that modulate the protease activity of an MTSP are provided. The invention also provides methods for recombinant prodn. of said polypeptides. The invention also provides antibodies and antisense oligonucleotides for MTSP, which inhibit the catalytic activity of MTSP and can be used as antitumor agents.

IC ICM C12N009-00
CC 7-8 (Enzymes)
Section cross-reference(s): 1, 3, 13
ST sequence cDNA human transmembrane serine **protease**; antitumor transmembrane serine **protease**; modulator transmembrane serine **protease**
IT Body fluid
(anal.; detection of human transmembrane serine **proteases** which differentially expressed in **tumor** subject and non-**tumor** subject)
IT Antibodies
RL: ANT (Analyte); BPR (Biological process); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)
(antibody for human transmembrane serine **proteases**)
IT EST (expressed sequence tag)
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(cDNA encoding human transmembrane serine **proteases**)
IT Antisense oligonucleotides
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cDNA encoding human transmembrane serine **proteases**)
IT cDNA sequences
(cDNA encoding human transmembrane serine **proteases**, their sequences, tissue distribution and use in therapeutics)
IT Neoplasm
(cells; differential expression of human transmembrane serine **proteases** in **tumor** cells and non-**tumor** cells)
IT Bacteria (Eubacteria)
Insect (Insecta)

Pichia
Yeast
(cells; recombinant host for expression of human transmembrane serine **proteases**)

IT Proteins, specific or class
RL: ANT (Analyte); ANST (Analytical study)
(conjugates; human transmembrane serine **proteases**, their sequences, tissue distribution, recombinant prodn. and therapeutic use)

IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(deletion or inactivation of endogenous gene of non-human animal transmembrane serine **proteases**)

IT Animal tissue
Ascitic fluid
Blood analysis
Cerebrospinal fluid
Saliva
Tear (ocular fluid)
Urine analysis
(detection of neoplastic disease in a biol. sample base on transmembrane serine **proteases**)

IT Immunoglobulins
RL: ANT (Analyte); BPR (Biological process); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)
(fragments; antibody for human transmembrane serine **proteases**)

IT Recombination, genetic
(homologous; deletion or inactivation of endogenous gene of non-human animal transmembrane serine **proteases**)

IT Angiogenesis inhibitors
Antitumor agents
Protein sequences
(human transmembrane serine **proteases**, their sequences, tissue distribution, recombinant prodn. and therapeutic use)

IT DNA microarray technology
(human transmembrane serine **proteases**, their sequences, use in microarray)

IT Peptidomimetics
(identification of compds. that modulate the **protease** activities of different human transmembrane serine **proteases**)

IT Natural products
Peptides, analysis
RL: ANT (Analyte); ANST (Analytical study)
(identification of compds. that modulate the **protease** activities of different human transmembrane serine **proteases**)

IT Body fluid
(interstitial; detection of neoplastic disease in a biol. sample base on transmembrane serine **proteases**)

IT **Antibodies**
RL: ANT (Analyte); BPR (Biological process); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)
(**monoclonal**; **antibody** for human transmembrane serine **proteases**)

IT Protein motifs
(**protease** domain; human transmembrane serine **proteases**, their sequences, tissue distribution, recombinant prodn. and therapeutic use)

IT Animal cell
Eukaryote (Eukaryotae)
Plant cell
Prokaryote
(recombinant host for expression of human transmembrane serine **proteases**)

IT Mutagenesis
(site-directed, deletion; deletion or inactivation of endogenous gene of non-human animal transmembrane serine **proteases**)
IT Mutagenesis
(site-directed, insertion; deletion or inactivation of endogenous gene of non-human animal transmembrane serine **proteases**)
IT Mutagenesis
(site-directed, substitution; cDNA encoding human transmembrane serine **proteases**)
IT 353752-73-5 353752-75-7 353752-76-8
RL: PRP (Properties)
(N-terminus sequence of human transmembrane serine **proteases**)
IT 353571-62-7DP, **Protease** MTSP3 (human) 353571-69-4P
RL: BOC (Biological occurrence); BPN (Biosynthetic preparation); PRP (Properties); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation); USES (Uses)
(amino acid sequence; human transmembrane serine **proteases**, their sequences, tissue distribution, recombinant prodn. and therapeutic use)
IT 239789-05-0P 242795-08-0P 353571-64-9P 353571-66-1P 353571-67-2P
RL: BOC (Biological occurrence); BPN (Biosynthetic preparation); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation); USES (Uses)
(amino acid sequence; human transmembrane serine **proteases**, their sequences, tissue distribution, recombinant prodn. and therapeutic use)
IT 354808-53-0P, Type-II membrane-type serine **proteinase** 3
RL: BOC (Biological occurrence); BPN (Biosynthetic preparation); PRP (Properties); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation); USES (Uses)
(human transmembrane serine **proteases**, their sequences, tissue distribution, recombinant prodn. and therapeutic use)
IT 9014-74-8P, Enteropeptidase 189121-13-9P, Human airway trypsin-like **proteinase** 241475-96-7P, Matriptase 244292-73-7P, Corin 252212-87-6P, **Proteinase**, TMPRSS2 354807-39-9P, **Proteinase** TMPRSS4 354808-55-2P, Type-II membrane-type serine **proteinase** 4 354808-57-4P, Type-II membrane-type serine **proteinase** 6
RL: BOC (Biological occurrence); BPN (Biosynthetic preparation); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation); USES (Uses)
(human transmembrane serine **proteases**, their sequences, tissue distribution, recombinant prodn. and therapeutic use)
IT 239789-04-9, Genbank AR081724 353571-61-6 353571-63-8 353571-65-0 353571-68-3 353810-97-6
RL: BOC (Biological occurrence); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(nucleotide sequence; cDNA encoding human transmembrane serine **proteases**, their sequences, tissue distribution and use in therapeutics)
IT 140030-70-2, GenBank M18930 157779-65-2 198056-06-3 208748-57-6 225721-84-6, DNA (human corin cDNA plus flanks) 255357-22-3, GenBank AF216312 340951-58-8 353578-88-8 353578-89-9 353578-90-2 353578-91-3 353578-92-4 353578-93-5 353578-94-6 353578-95-7 353578-96-8 353578-97-9 353578-98-0 353578-99-1 353579-00-7 353579-01-8 353579-02-9 353579-03-0 353579-04-1 353579-05-2 353579-06-3 353579-07-4 353579-08-5 353579-09-6 353579-10-9 353579-11-0 353579-12-1 353579-13-2 353579-14-3 353579-15-4 353579-16-5 353579-17-6 353579-18-7 353579-19-8 353579-20-1 353579-21-2 353579-22-3 353579-23-4 353579-24-5 353579-25-6
RL: PRP (Properties)
(unclaimed nucleotide sequence; cDNA encoding human transmembrane serine **proteases**)

IT 112398-26-2, Hepsin (human liver clone HepG2UW7/HUW1250 precursor reduced) 157909-67-6 175336-92-2 197982-63-1 244295-79-2, Corin (human precursor) 334069-13-5 353579-26-7 354133-83-8
RL: PRP (Properties)
(unclaimed protein sequence; cDNA encoding human transmembrane serine **proteases**)
IT 354133-87-2
RL: PRP (Properties)
(unclaimed sequence; cDNA encoding human transmembrane serine **proteases**)

L25 ANSWER 2 OF 18 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:396524 CAPLUS
DOCUMENT NUMBER: 135:1281
TITLE: Vectors capable of immortalizing non-dividing cells, cells immortalized with said vectors and their use
INVENTOR(S): Occhidoro, Teresa; Salmon, Patrick; Trono, Didier
PATENT ASSIGNEE(S): Universite de Geneve, Switz.
SOURCE: Eur. Pat. Appl., 26 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1103615	A1	20010530	EP 1999-123498	19991125
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
WO 2001038548	A2	20010531	WO 2000-EP11723	20001124
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.: EP 1999-123498 A 19991125

AB A vector encoding at least one immortalization mol. which is capable of transporting a transgene into the nucleus of a slowly growing or nondividing cell and stably integrating said transgene into the genome of the cell is disclosed. Immortalized cells produced with such vectors and the use of these cells, e.g., immortalized .beta. cells to prep. an artificial pancreas, to immortalized keratinocytes to produce skin, or immortalized B cells produce monoclonal antibodies, are also disclosed. Thus, HIV-1-based vectors encoding the SV40 large T antigen or telomerase were used to immortalized liver sinusoidal endothelial cells. These cells have been maintained in culture for 9 mo (>60 passages) and have maintained features typical of these cells. The vectors contain loxP sites so that the immortalizing gene can be removed upon exposure to Cre recombinase.

IC ICM C12N015-63
ICS C12N015-64; C12N005-16; C12N005-22; C12N007-01; C12P021-00
CC 3-5 (Biochemical Genetics)
IT Anti-infective agents
Antitumor agents
(immortalized dendritic cells and; vectors capable of immortalizing non-dividing cells, cells immortalized with said vectors and their use)
IT B cell (lymphocyte)
(immortalized, **monoclonal antibody** prodn. with;

vectors capable of immortalizing non-dividing cells, cells immortalized with said vectors and their use)

IT **Antibodies**
RL: BMF (Bioindustrial manufacture); BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(**monoclonal**, immortalized B cells for prodn. of; vectors capable of immortalizing non-dividing cells, cells immortalized with said vectors and their use)

IT Bovine immunodeficiency virus
Caprine arthritis encephalitis virus
Equine infectious anemia virus
Feline immunodeficiency virus
Gibbon ape leukemia virus
Harvey murine **sarcoma** virus
Human immunodeficiency virus
Human immunodeficiency virus 1
Lentivirus
Mouse mammary **tumor** virus
Murine leukemia virus
Rous **sarcoma** virus
Simian immunodeficiency virus
Visna-Maedi virus
(vectors; vectors capable of immortalizing non-dividing cells, cells immortalized with said vectors and their use)

IT 9001-92-7, **Protease** 9068-38-6, Reverse transcriptase
52350-85-3, Integrase 120178-12-3, Telomerase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(viral vector encoding; vectors capable of immortalizing non-dividing cells, cells immortalized with said vectors and their use)

REFERENCE COUNT: 9
REFERENCE(S):
(1) Chabot, B; WO 9800537 A 1998 CAPLUS
(2) Gallay, P; WO 9812314 A 1998 CAPLUS
(3) Genetix Pharmaceuticals Inc; WO 9958701 A 1999 CAPLUS
(4) Miyoshi, H; JOURNAL OF VIROLOGY 1998, V72(10), P8150 CAPLUS
(6) Salk Inst For Biological Studi; WO 9712622 A 1997 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 3 OF 18 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:380745 CAPLUS
DOCUMENT NUMBER: 135:16024
TITLE: Cloning, expression, characterization and diagnostic, therapeutic and screening use of human endotheliase isoenzymes
INVENTOR(S): Madison, Edwin L.; Ong, Edgar O.
PATENT ASSIGNEE(S): Corvas International, Inc., USA
SOURCE: PCT Int. Appl., 152 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001036604	A2	20010525	WO 2000-US31803	20001117

W: AE, AG, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU,

ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-166391 P 19991118
US 2000-234840 P 20000922

AB Provided herein endotheliases (transmembrane serine proteases) and portions, particularly, the protease domains, and nucleic acids that encode the endotheliases. The endotheliases are transmembrane proteases expressed in endothelial cells. Cloning, expression, and cDNA and encoded amino acid sequences of human endotheliase 1, endotheliase 2-S and endotheliase 2-L are disclosed. The nucleic acids and encoded proteins and protease domain portions thereof are used in a variety of prognostic, diagnostic, therapeutic and screening methods, including methods for screening for compds. that modulate angiogenesis.

IC ICM C12N009-00
CC 7-5 (Enzymes)
Section cross-reference(s): 1, 3, 13
ST endotheliase isoenzyme cDNA sequence angiogenesis modulator screening; endothelial cell **protease** domain endotheliase isoenzyme sequence
IT Mammary gland
(**carcinoma**; cloning, expression, characterization and diagnostic, therapeutic and screening use of human endotheliase isoenzymes)
IT Angiogenesis inhibitors
Anti-inflammatory agents
Antitumor agents
Antiulcer agents
Atherosclerosis
Blindness
Blood vessel, disease
Cirrhosis
Diabetes mellitus
Drug screening
Drug targeting
Endothelium
Eye, disease
Gene therapy
Genetic mapping
Genetic vectors
Granulation tissue
Mammal (Mammalia)
Molecular cloning
Mutagenesis
Mutation
Placenta
Protein sequences
Psoriasis
Rheumatoid arthritis
Skin, disease
Test kits
cDNA sequences
(cloning, expression, characterization and diagnostic, therapeutic and screening use of human endotheliase isoenzymes)
IT **Antibodies**
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**monoclonal**; cloning, expression, characterization and diagnostic, therapeutic and screening use of human endotheliase isoenzymes)
IT 342607-01-6D, Serine **protease**, conjugates with targeting agent
342607-66-3D, Endotheliase 2-S, conjugates with targeting agent

342607-68-5D, Endotheliase 2-L, conjugates with targeting agent
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cloning, expression, characterization and diagnostic, therapeutic and screening use of human endotheliase isoenzymes)

L25 ANSWER 4 OF 18 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:380438 CAPLUS
DOCUMENT NUMBER: 135:24657
TITLE: Selective cellular targeting: multifunctional delivery vehicles
INVENTOR(S): Glazier, Arnold
PATENT ASSIGNEE(S): Drug Innovation + Design, Inc., USA
SOURCE: PCT Int. Appl., 981 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001036003	A2	20010525	WO 2000-US31262	20001114

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-165485 P 19991115
US 2000-239478 P 20001011
US 2000-241939 P 20001020

AB The present invention relates to the compns., methods, and applications of a novel approach to selective cellular targeting. The purpose of this invention is to enable the selective delivery and/or selective activation of effector mols. to target cells for diagnostic or therapeutic purposes. The present invention relates to multi-functional prodrugs or targeting vehicles wherein each functionality is capable of enhancing targeting selectivity, affinity, intracellular transport, activation or detoxification. The present invention also relates to ultralow dose, multiple target, multiple drug chemotherapy and targeted immunotherapy for cancer treatment.

IC ICM A61K047-48
CC 63-5 (Pharmaceuticals)
Section cross-reference(s): 1, 2, 8, 15, 25, 28
IT **Antibodies**
RL: BPR (Biological process); PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(**monoclonal**; multifunctional delivery vehicles for selective cellular targeting of drugs)
IT **Antitumor agents**
Cell division
Chelating agents
Cytotoxic agents
Drug targeting
Imaging agents
Immunization
Immunostimulants
(multifunctional delivery vehicles for selective cellular targeting of drugs)

IT Antigens
RL: BOC (Biological occurrence); BPR (Biological process); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(**tumor**-assocd.; multifunctional delivery vehicles for selective cellular targeting of drugs)
IT Vaccines
(**tumor**; multifunctional delivery vehicles for selective cellular targeting of drugs)
IT **Antitumor agents**
(vaccines; multifunctional delivery vehicles for selective cellular targeting of drugs)
IT 9001-12-1, Collagenase 9001-77-8 9001-92-7, **Proteinase** 9002-07-7, Trypsin 9004-06-2, MMP 12 9004-08-4, Cathepsin 9025-26-7, Cathepsin d 9025-62-1, Steroid sulfatase 9030-23-3, Thymidine phosphorylase 9031-61-2, Thymidylate synthase 9039-53-6, Urokinase 9040-48-6, Gelatinase 9045-77-6, Fatty acid synthase 9047-22-7, Cathepsin b 9074-87-7, Glutamate carboxypeptidase II 60616-82-2, Cathepsin L 62229-50-9, Egf 79955-99-0, MMP-3 84419-03-4, Guanidinobenzoatase 94716-09-3, Cathepsin k 115926-52-8, Phosphatidylinositol 3-kinase 141256-52-2, Matrilysin 141907-41-7, Matrix metalloproteinase 142008-29-5, Protein kinase a 142243-02-5, Map kinase 142805-58-1, Map kinase kinase 145267-01-2, Stromelysin 3 146480-35-5, MMP 2 162032-86-2, Cathepsin O 175449-82-8, MMP-13 241475-96-7, Matriptase
RL: BOC (Biological occurrence); BPR (Biological process); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(multifunctional delivery vehicles for selective cellular targeting of drugs)

L25 ANSWER 5 OF 18 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:208111 CAPLUS
DOCUMENT NUMBER: 134:247241
TITLE: Methods and compositions for modulating responsiveness to corticosteroids
INVENTOR(S): Sekut, Les; Carter, Adam; Ghayur, Tariq; Banerjee, Subhashis; Tracey, Daniel E.
PATENT ASSIGNEE(S): BASF A.-G., Germany
SOURCE: PCT Int. Appl., 151 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001019373	A2	20010322	WO 2000-US24725	20000908
WO 2001019373	A3	20011004		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-398555 A1 19990917
AB Methods for modulating responsiveness to corticosteroids in a subject are provided. An agent which antagonizes a target that regulates prodn. of IFN-.gamma. in the subject is administered to the subject in combination with a corticosteroid such that responsiveness of the subject to the corticosteroid is modulated as compared to when a corticosteroid alone is

administered to the subject. In one embodiment, the agent is an IL-18 antagonist. In another embodiment, the agent is an interleukin-12 (IL-12) antagonist. In yet another embodiment, the agent is an NK cell antagonist. In a preferred embodiment, the agent is an inhibitor of a caspase family protease, preferably an ICE inhibitor. In another preferred embodiment, the agent is an anti-IL-12 monoclonal antibody. In yet another preferred embodiment, the agent is an anti-asialo-GM1 antibody or an NK1.1 antibody. Other preferred agents include phosphodiesterase IV inhibitors and beta-2 agonists. The methods of the invention can be used in the treatment of a variety of inflammatory and immunol. diseases and disorders. Pharmaceutical compns. comprising an agent which antagonizes a target that regulates prodn. of IFN-.gamma. in a subject, a corticosteroid and a pharmaceutically acceptable carrier are also provided. A preferred compn. comprises an ICE inhibitor, a corticosteroid and a pharmaceutically acceptable carrier.

IC ICM A61K031-57

CC 1-7 (Pharmacology)
Section cross-reference(s): 25, 63

ST corticosteroid responsiveness modulator inflammation immune disease; interferon prodn corticosteroid responsiveness modulator; interleukin antagonist corticosteroid responsiveness modulator; NK cell antagonist corticosteroid responsiveness modulator; caspase inhibitor corticosteroid responsiveness modulator; ICE inhibitor corticosteroid responsiveness modulator; phosphodiesterase inhibitor corticosteroid responsiveness modulator; beta2 adrenergic agonist corticosteroid responsiveness modulator; **monoclonal antibody** corticosteroid responsiveness modulator

IT Interleukin 1.alpha.
Interleukin 1.beta.
Tumor necrosis factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(antibody to; methods and compns. for modulating responsiveness to corticosteroids)

IT **Antitumor agents**
(leukemia; methods and compns. for modulating responsiveness to corticosteroids)

IT **Antibodies**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**monoclonal**; methods and compns. for modulating responsiveness to corticosteroids)

IT 9001-92-7, **Protease**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(caspase-family, inhibitors; methods and compns. for modulating responsiveness to corticosteroids)

IT 9036-21-9, Phosphodiesterase IV 128028-50-2, **Proteinase** PR3 182762-08-9, Caspase 4 186322-81-6, Caspase 192465-11-5, Caspase 5
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; methods and compns. for modulating responsiveness to corticosteroids)

IT 169592-56-7, CPP32 **proteinase** 182372-14-1, ICH-1 **proteinase** 182372-15-2, Caspase Mch2 189258-14-8, **Proteinase** Mch3
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(methods and compns. for modulating responsiveness to corticosteroids)

IT 122191-40-6, ICE **proteinase**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(methods and compns. for modulating responsiveness to corticosteroids)

L25 ANSWER 6 OF 18 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:168148 CAPLUS

DOCUMENT NUMBER: 134:218930
TITLE: Human serine **protease** inhibitor headpin and its gene and diagnostic and therapeutic uses
INVENTOR(S): Clayman, Gary L.; Nakashima, Torahiko; Spring, Paul M.
PATENT ASSIGNEE(S): Board of Regents, the University of Texas System, USA
SOURCE: PCT Int. Appl., 213 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001016324	A2	20010308	WO 2000-US24214	20000831

W: CA, JP
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

PRIORITY APPLN. INFO.: US 1999-151776 P 19990831

AB The present invention describes a novel gene encoding a novel protein termed headpin (for head and neck serpin) that is homologous to known serine protease inhibitors. Headpin is a differentially expressed, novel serine proteinase inhibitor that belongs to the ov-serpin family and demonstrates a hinge region consensus sequence that predicts an inhibitory function. Headpin was cloned from a keratinocyte cDNA library, and its expression pattern by Northern blot anal. indicates that it is most likely produced by keratinizing epithelium. The endogenous expression headpin in normal oral keratinocytes, and its absence or down-regulation in squamous cell carcinoma of the oral cavity, supports the involvement of headpin as a marker for squamous differentiation or a gene disadvantageous to tumor function. Headpin has been grouped into the cluster of serpins located at chromosome 18q21.3/18q22. This region is a known area for loss of heterozygosity and other deletional events often assocd. with head and neck cancer. The invention describes methods and compns. of the nucleic acids, encoded proteins, antibodies, pharmaceuticals, cancer treatments, diagnostics and screens for modulators of headpin.

IC ICM C12N015-15
ICS C07K014-81; C12N015-11; C12N005-10; A61K038-57; A61K048-00; C12Q001-68; G01N033-53

CC 7-3 (Enzymes)
Section cross-reference(s): 3, 13, 63

ST headpin **proteinase** inhibitor cDNA sequence human; **tumor** headpin **proteinase** inhibitor

IT Hybridoma
(antibody-producing; human serine **protease** inhibitor headpin and its gene and diagnostic and therapeutic uses)

IT Diagnosis
(cancer; human serine **protease** inhibitor headpin and its gene and diagnostic and therapeutic uses)

IT Intestine, neoplasm
(colon, diagnosis and treatment of; human serine **protease** inhibitor headpin and its gene and diagnostic and therapeutic uses)

IT Brain, neoplasm
Kidney, neoplasm
Leukemia
Liver, neoplasm
Lung, neoplasm
Ovary, neoplasm
Pancreas, neoplasm
Skin, neoplasm
Spleen, neoplasm
Stomach, neoplasm
Testis, neoplasm

(diagnosis and treatment of; human serine **protease** inhibitor headpin and its gene and diagnostic and therapeutic uses)

IT Neoplasm
(diagnosis; human serine **protease** inhibitor headpin and its gene and diagnostic and therapeutic uses)

IT Uterus, neoplasm
(endometrium, diagnosis and treatment of; human serine **protease** inhibitor headpin and its gene and diagnostic and therapeutic uses)

IT Immunoassay
(enzyme-linked immunosorbent assay; human serine **protease** inhibitor headpin and its gene and diagnostic and therapeutic uses)

IT cDNA sequences
(for human serine **protease** inhibitor headpin)

IT Gene, animal
RL: BOC (Biological occurrence); BPR (Biological process); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(headpin; human serine **protease** inhibitor headpin and its gene and diagnostic and therapeutic uses)

IT Chromosome
(human 18, headpin gene mapping on chromosome 18q21.3; human serine **protease** inhibitor headpin and its gene and diagnostic and therapeutic uses)

IT **Antitumor agents**
Gene therapy
Immunoassay
Molecular cloning
Nucleic acid amplification (method)
Retroviral vectors
Virus vectors
(human serine **protease** inhibitor headpin and its gene and diagnostic and therapeutic uses)

IT Antibodies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(human serine **protease** inhibitor headpin and its gene and diagnostic and therapeutic uses)

IT Promoter (genetic element)
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(human serine **protease** inhibitor headpin and its gene and diagnostic and therapeutic uses)

IT Antisense DNA
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(human serine **protease** inhibitor headpin and its gene and diagnostic and therapeutic uses)

IT **Antibodies**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**monoclonal**; human serine **protease** inhibitor headpin and its gene and diagnostic and therapeutic uses)

IT Bone marrow, disease
Esophagus
Mammary gland
Prostate gland
(neoplasm, diagnosis and treatment of; human serine **protease** inhibitor headpin and its gene and diagnostic and therapeutic uses)

IT Lymph node
(neoplasm, metastasis, diagnosis and treatment of; human serine **protease** inhibitor headpin and its gene and diagnostic and therapeutic uses)

IT Genetic mapping
(of headpin gene on chromosome 18q21.3; human serine **protease** inhibitor headpin and its gene and diagnostic and therapeutic uses)

IT Protein sequences
(of human serine **protease** inhibitor headpin)

IT Genetic element
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(polyadenylation signal; human serine **protease** inhibitor headpin and its gene and diagnostic and therapeutic uses)
IT Intestine, neoplasm
(small, diagnosis and treatment of; human serine **protease** inhibitor headpin and its gene and diagnostic and therapeutic uses)
IT Head
Neck, anatomical
(squamous cell **carcinoma**, diagnosis and treatment of; human serine **protease** inhibitor headpin and its gene and diagnostic and therapeutic uses)
IT Adeno-associated virus
Adenoviridae
Herpesviridae
Vaccinia virus
(vectors; human serine **protease** inhibitor headpin and its gene and diagnostic and therapeutic uses)
IT 244614-96-8D, GenBank AF169949-derived protein GI 5911369, subfragments are claimed 329335-44-6D, subfragments are claimed 329335-45-7D, subfragments are claimed
RL: BOC (Biological occurrence); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(amino acid sequence; human serine **protease** inhibitor headpin and its gene and diagnostic and therapeutic uses)
IT 252966-50-0, Headpin **proteinase** inhibitor
RL: BOC (Biological occurrence); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(human serine **protease** inhibitor headpin and its gene and diagnostic and therapeutic uses)
IT 240796-67-2D, GenBank AF169949, subfragments are claimed 329165-54-0D, subfragments are claimed 329165-55-1D, subfragments are claimed
RL: BOC (Biological occurrence); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(nucleotide sequence; human serine **protease** inhibitor headpin and its gene and diagnostic and therapeutic uses)
IT 180771-43-1 329335-54-8 329335-55-9
RL: PRP (Properties)
(unclaimed nucleotide sequence; human serine **protease** inhibitor headpin and its gene and diagnostic and therapeutic uses)
IT 108570-68-9 171546-83-1 223248-90-6 329335-53-7 329348-07-4 329348-72-3
RL: PRP (Properties)
(unclaimed protein sequence; human serine **protease** inhibitor headpin and its gene and diagnostic and therapeutic uses)
IT 329307-62-2 329307-63-3 329307-64-4 329307-65-5 329307-66-6 329307-67-7
RL: PRP (Properties)
(unclaimed sequence; human serine **protease** inhibitor headpin and its gene and diagnostic and therapeutic uses)

L25 ANSWER 7 OF 18 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:101193 CAPLUS
DOCUMENT NUMBER: 134:161887
TITLE: Compositions and methods for the treatment of **tumors**
INVENTOR(S): Bodary, Sarah C.; Fisher, Karen L.
PATENT ASSIGNEE(S): Genentech, Inc., USA
SOURCE: PCT Int. Appl., 118 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001009189	A2	20010208	WO 2000-US20731	20000727
WO 2001009189	A3	20010614		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-146217 P 19990728

AB The invention concerns compns. and methods for the diagnosis and treatment of neoplastic cell growth and proliferation in mammals, including humans. The invention is based upon the identification of an ADAM8 gene that is amplified in the genome of tumor cells. Such gene amplification is assocd. with the overexpression of the gene product as compared to normal cells of the same tissue type and contributes to tumorigenesis. Accordingly, the ADAM8 protein encoded by the amplified gene is a useful target for the diagnosis and/or treatment (including prevention) of certain cancers, and acts as a predictor of the prognosis of tumor treatment.

IC ICM C07K016-00
CC 15-3 (Immunochemistry)
Section cross-reference(s): 3, 9, 14, 63
ST ADAM8 protein gene **monoclonal antibody** cancer; cancer diagnosis therapy antisense oligonucleotide ADAM8 gene
IT Animal tissue culture
Antitumor agents
Buffers
Chemotherapy
Cytotoxic agents
DNA sequences
Drug screening
Fluorometry
Genetic vectors
Labels
Mammal (Mammalia)
Microscopy
Molecular cloning
Nucleic acid hybridization
Protein sequences
Radiotherapy
(ADAM8 polypeptide and gene and antibodies for diagnosis and treatment of **tumors**)
IT Antibodies
Antisense oligonucleotides
DNA
Nucleic acids
Probes (nucleic acid)
Ribozymes
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ADAM8 polypeptide and gene and antibodies for diagnosis and treatment of **tumors**)
IT Gene, animal
Proteins, specific or class
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified);

PRP (Properties); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(ADAM8; ADAM8 polypeptide and gene and antibodies for diagnosis and treatment of **tumors**)

IT Quaternary structure
(DNA triplex; ADAM8 polypeptide and gene and antibodies for diagnosis and treatment of **tumors**)

IT Antibodies
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anti-idiotypic; ADAM8 polypeptide and gene and antibodies for diagnosis and treatment of **tumors**)

IT Diagnosis
(cancer; ADAM8 polypeptide and gene and antibodies for diagnosis and treatment of **tumors**)

IT Drug delivery systems
(carriers; ADAM8 polypeptide and gene and antibodies for diagnosis and treatment of **tumors**)

IT Medical goods
(containers; ADAM8 polypeptide and gene and antibodies for diagnosis and treatment of **tumors**)

IT Neoplasm
(diagnosis; ADAM8 polypeptide and gene and antibodies for diagnosis and treatment of **tumors**)

IT Test kits
(diagnostic; ADAM8 polypeptide and gene and antibodies for diagnosis and treatment of **tumors**)

IT Cytometry
(flow; ADAM8 polypeptide and gene and antibodies for diagnosis and treatment of **tumors**)

IT Immunoglobulins
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fragments; ADAM8 polypeptide and gene and antibodies for diagnosis and treatment of **tumors**)

IT Fusion proteins (chimeric proteins)
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(humanized antibodies; ADAM8 polypeptide and gene and antibodies for diagnosis and treatment of **tumors**)

IT Diagnosis
(immunodiagnosis; ADAM8 polypeptide and gene and antibodies for diagnosis and treatment of **tumors**)

IT Cell death
(induction; ADAM8 polypeptide and gene and antibodies for diagnosis and treatment of **tumors**)

IT Containers
(medical; ADAM8 polypeptide and gene and antibodies for diagnosis and treatment of **tumors**)

IT Neoplasm
(metastasis, diagnosis and treatment; ADAM8 polypeptide and gene and antibodies for diagnosis and treatment of **tumors**)

IT **Antibodies**
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**monoclonal**; ADAM8 polypeptide and gene and **antibodies** for diagnosis and treatment of **tumors**)

IT Matrix media
(solid support; ADAM8 polypeptide and gene and antibodies for diagnosis and treatment of **tumors**)

IT 252351-00-1P, **Proteinase**, metallo-, ADAM8
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); PUR (Purification or recovery); THU (Therapeutic use);

BIOL (Biological study); PREP (Preparation); USES (Uses)
(ADAM8 polypeptide and gene and antibodies for diagnosis and treatment of **tumors**)

IT 325497-90-3 325497-91-4 325497-92-5 325497-93-6 325497-94-7
325497-95-8 325497-96-9 325497-97-0 325497-98-1 325497-99-2
325498-00-8
RL: BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ADAM8 polypeptide and gene and antibodies for diagnosis and treatment of **tumors**)

IT 189305-01-9, Antigen CD156 (human precursor reduced)
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(amino acid sequence; ADAM8 polypeptide and gene and antibodies for diagnosis and treatment of **tumors**)

IT 325501-97-1, DNA (human metalloproteinase ADAM8 gene)
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(nucleotide sequence; ADAM8 polypeptide and gene and antibodies for diagnosis and treatment of **tumors**)

IT 325503-33-1 325503-34-2 325503-35-3 325503-36-4
RL: PRP (Properties)
(unclaimed nucleotide sequence; compns. and methods for the treatment of **tumors**)

IT 325172-50-7 325172-51-8 325172-52-9 325172-53-0 325172-54-1
RL: PRP (Properties)
(unclaimed sequence; compns. and methods for the treatment of **tumors**)

L25 ANSWER 8 OF 18 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:12622 CAPLUS
DOCUMENT NUMBER: 134:96260
TITLE: Human lung **tumor**-associated proteins and their encoding nucleic acids for the therapy and diagnosis of lung cancer
INVENTOR(S): Wang, Tongtong; Bangur, Chaitanya S.; Lodes, Michael J.; Fanger, Gary R.; Vedvick, Thomas S.; Carter, Darrick; Retter, Marc W.; Mannion, Jane
PATENT ASSIGNEE(S): Corixa Corporation, USA
SOURCE: PCT Int. Appl., 436 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001000828	A2	20010104	WO 2000-US18061	20000630
WO 2001000828	A3	20010802		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:
US 1999-346492 A 19990630
US 1999-419356 A 19991015
US 1999-466867 A 19991217
US 1999-476300 A 19991230

US 2000-519642 A 20000306
US 2000-533077 A 20000322
US 2000-546259 A 20000410
US 2000-560406 A 20000427
US 2000-589184 A 20000605

AB Compns. and methods for the therapy and diagnosis of cancer, such as lung cancer, are disclosed. Lung tumor protein cDNAs were isolated and characterized from cDNA libraries isolated from lung adenocarcinoma, small cell lung carcinoma, lung neuroendocrine carcinoma, or squamous cell lung carcinoma using conventional cDNA library subtraction and PCR-based cDNA library subtraction. Compns. may comprise one or more lung tumor proteins, immunogenic portions thereof, or polynucleotides that encode such portions. Alternatively, a therapeutic compn. may comprise an antigen presenting cell that expresses a lung tumor protein, or a T cell that is specific for cells expressing such a protein. Such compns. may be used, for example, for the prevention and treatment of diseases such as lung cancer. Diagnostic methods based on detecting a lung tumor protein, or mRNA encoding such a protein, in a sample are also provided.

IC ICM C12N015-12
ICS C07K014-47; C07K014-705; C07K016-18; C12N015-62; A61K038-17; C12Q001-68

CC 3-3 (Biochemical Genetics)
Section cross-reference(s): 6, 14, 63

ST lung **tumor** protein cDNA sequence human; cancer diagnosis therapy lung **tumor** protein cDNA

IT Proteins, specific or class
RL: ARG (Analytical reagent use); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(A, fusion products as detection reagents; human lung **tumor** -assocd. proteins and their encoding nucleic acids for the therapy and diagnosis of lung cancer)

IT Proteins, specific or class
RL: ARG (Analytical reagent use); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(G, fusion products as detection reagents; human lung **tumor** -assocd. proteins and their encoding nucleic acids for the therapy and diagnosis of lung cancer)

IT Lung, neoplasm
(adenocarcinoma; human lung **tumor**-assocd. proteins and their encoding nucleic acids for the therapy and diagnosis of lung cancer)

IT Nucleic acid hybridization
PCR (polymerase chain reaction)
(assay for mRNA; human lung **tumor**-assocd. proteins and their encoding nucleic acids for the therapy and diagnosis of lung cancer)

IT Diagnosis
(cancer; human lung **tumor**-assocd. proteins and their encoding nucleic acids for the therapy and diagnosis of lung cancer)

IT Lung, neoplasm
(**carcinoma**, neuroepithelial body; human lung **tumor** -assocd. proteins and their encoding nucleic acids for the therapy and diagnosis of lung cancer)

IT Test kits
(diagnostic; human lung **tumor**-assocd. proteins and their encoding nucleic acids for the therapy and diagnosis of lung cancer)

IT cDNA sequences
(for human lung **tumor**-assocd. proteins)

IT Agglutinins and Lectins
RL: ARG (Analytical reagent use); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(fusion products as detection reagents; human lung **tumor** -assocd. proteins and their encoding nucleic acids for the therapy and diagnosis of lung cancer)

IT Antigen-presenting cell

Dendritic cell
Gene therapy
Immunoassay
Immunostimulants
Macrophage
Molecular cloning
(human lung **tumor**-assocd. proteins and their encoding nucleic acids for the therapy and diagnosis of lung cancer)

IT Antibodies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(human lung **tumor**-assocd. proteins and their encoding nucleic acids for the therapy and diagnosis of lung cancer)

IT Lung, neoplasm
(inhibitors; human lung **tumor**-assocd. proteins and their encoding nucleic acids for the therapy and diagnosis of lung cancer)

IT **Antitumor agents**
(lung; human lung **tumor**-assocd. proteins and their encoding nucleic acids for the therapy and diagnosis of lung cancer)

IT **Antibodies**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**monoclonal**; human lung **tumor**-assocd. proteins and their encoding nucleic acids for the therapy and diagnosis of lung cancer)

IT Protein sequences
(of human lung **tumor**-assocd. proteins)

IT Lung, neoplasm
(small-cell **carcinoma**; human lung **tumor**-assocd. proteins and their encoding nucleic acids for the therapy and diagnosis of lung cancer)

IT Lung, neoplasm
(squamous cell **carcinoma**; human lung **tumor**-assocd. proteins and their encoding nucleic acids for the therapy and diagnosis of lung cancer)

IT T cell (lymphocyte)
(stimulation of specific; human lung **tumor**-assocd. proteins and their encoding nucleic acids for the therapy and diagnosis of lung cancer)

IT Proteins, specific or class
RL: ANT (Analyte); BOC (Biological occurrence); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(**tumor**-assocd.; human lung **tumor**-assocd. proteins and their encoding nucleic acids for the therapy and diagnosis of lung cancer)

IT Fusion proteins (chimeric proteins)
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(with T helper epitope or affinity tag; human lung **tumor**-assocd. proteins and their encoding nucleic acids for the therapy and diagnosis of lung cancer)

IT 120147-21-9, Ribonucleoprotein (human clone LH88 small nuclear RNA-containing protein E subunit) 120432-79-3 122319-34-0, Glycoprotein IGF-BP 3 (human clone ibp.118 precursor protein moiety reduced) 130704-71-1, RNA formation factor (human fibroblast gene Egr-1 reduced) 139317-02-5, Protein CRABP-II (human clone .lambda.f1.1 reduced) 143178-20-5, **Proteinase** (human deblocked subunit .nu. reduced) 150789-86-9 156288-41-4 168183-32-2 169241-54-7 196624-84-7, Phosphoprotein HMG2 (human gene HMG2a) 214774-02-4 220752-31-8 233671-98-2 245058-19-9 287984-48-9 317397-56-1 317397-57-2 317402-11-2 317402-12-3 317402-13-4 317402-15-6 317402-19-0 317402-20-3 317402-26-9 317402-27-0 317402-30-5 317402-48-5 317807-07-1
RL: ANT (Analyte); BOC (Biological occurrence); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); OCCU

(Occurrence); USES (Uses)
(amino acid sequence; human lung **tumor**-assocd. proteins and their encoding nucleic acids for the therapy and diagnosis of lung cancer)

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RL: ANT (Analyte); BOC (Biological occurrence); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(nucleotide sequence; human lung **tumor**-assocd. proteins and their encoding nucleic acids for the therapy and diagnosis of lung cancer)

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RL: ANT (Analyte); BOC (Biological occurrence); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); OCCU (Occurrence); USES (Uses)

(nucleotide sequence; human lung **tumor**-assocd. proteins and their encoding nucleic acids for the therapy and diagnosis of lung cancer)

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RL: ANT (Analyte); BOC (Biological occurrence); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(nucleotide sequence; human lung **tumor**-assocd. proteins and their encoding nucleic acids for the therapy and diagnosis of lung cancer)

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317402-37-2 317402-38-3 317402-39-4 317402-40-7 317402-41-8
317402-42-9 317402-43-0 317402-44-1 317402-45-2 317402-46-3
317402-47-4
RL: ANT (Analyte); BOC (Biological occurrence); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(nucleotide sequence; human lung **tumor**-assocd. proteins and their encoding nucleic acids for the therapy and diagnosis of lung cancer)

L25 ANSWER 9 OF 18 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:814262 CAPLUS
DOCUMENT NUMBER: 133:366416
TITLE: Nucleic acid-antibody conjugate for delivering a foreign nucleic acid in cells
INVENTOR(S): Hirsch, Francois; Durrbach, Antoine
PATENT ASSIGNEE(S): Centre National de la Recherche Scientifique (CNRS), Fr.
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000067697	A2	20001116	WO 2000-FR1259	20000510
WO 2000067697	A3	20010628		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
FR 2793414	A1	20001117	FR 1999-5943	19990510

PRIORITY APPLN. INFO.: FR 1999-5943 A 19990510

AB The invention concerns the techniques related to the insertion of foreign nucleic acid in cells. More particularly, it concerns a DNA-antibody conjugate enabling an efficient foreign DNA expression in vivo or in vitro in protein form in target cells.

IC ICM A61K
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 15
IT Peptides, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(glycolytic or **proteolytic** enzyme-cleavable; nucleic acid-antibody conjugate for delivery of foreign nucleic acid to cell)
IT **Antibodies**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**monoclonal**, conjugates; nucleic acid-**antibody** conjugate for delivery of foreign nucleic acid to cell)
IT Anti-infective agents
Antitumor agents
Coupling agents
Drug delivery systems
Drug targeting
Gene therapy
Replicon
Therapy
Transformation, genetic
(nucleic acid-antibody conjugate for delivery of foreign nucleic acid to cell)
IT Kidney, neoplasm
(renal cell **carcinoma**, cell; nucleic acid-antibody conjugate for delivery of foreign nucleic acid to cell)
IT Kidney, neoplasm
(renal cell **carcinoma**, inhibitors; nucleic acid-antibody conjugate for delivery of foreign nucleic acid to cell)

IT **Antitumor agents**
(renal cell **carcinoma**; nucleic acid-antibody conjugate for delivery of foreign nucleic acid to cell)
IT 9001-92-7, **Protease**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(peptide cleavable by; nucleic acid-antibody conjugate for delivery of foreign nucleic acid to cell)

L25 ANSWER 10 OF 18 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:368577 CAPLUS
DOCUMENT NUMBER: 133:14080
TITLE: Cloning of cDNA for novel serine **protease** BSSP6 from human and mice, and immunoassay of BSSP6 for diagnosis
INVENTOR(S): Uemura, Hidetoshi; Okui, Akira; Kominami, Katsuya; Yamaguchi, Nozomi; Mitsui, Shinichi
PATENT ASSIGNEE(S): Fuso Pharmaceutical Industries, Ltd., Japan
SOURCE: PCT Int. Appl., 94 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000031257	A1	20000602	WO 1999-JP6476	19991119
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1132473	A1	20010912	EP 1999-972681	19991119
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.: JP 1998-347802 A 19981120
WO 1999-JP6476 W 19991119

AB The cDNA encoding for a novel serine protease BSSP6 have been isolated from a brain cDNA library of human and mice, resp. Also claimed are the transgenic non-human animals with altered expression level of a serine protease BSSP6; an antibody against BSSP6; and a method for detecting BSSP6 in a specimen by using the antibody. The BSSP6 thus provided is usable in treating and diagnosing various diseases such as Alzheimer's disease, epilepsy, cancer, inflammation, sterility and prostatic hypertrophy and detecting pancreatitis in various tissues including brain, prostate gland, placenta, testis, pancreas and spleen.
IC ICM C12N015-12
ICS C12N009-64; C12N005-06; C12N001-21; C07K016-40; C12P021-08; A01K067-027; G01N033-543
CC 7-2 (Enzymes)
Section cross-reference(s): 3, 13, 15
ST human mouse cDNA sequence **protease** BSSP5; serine **protease** BSSP5 immunoassay diagnosis; prostate brain placenta testis pancreas spleen BSSP5 immunodiagnosis
IT Animal cell line
(PC-3; of human prostate **tumor**; cloning of cDNA for novel serine **protease** BSSP6 from human and mice, and immunoassay of BSSP6 for diagnosis)

IT Prostate gland
(benign hyperplasia, transgenic; BSSP6 expression in; cloning of cDNA for novel serine **protease** BSSP6 from human and mice, and immunoassay of BSSP6 for diagnosis)
IT Diagnosis
(cancer; cloning of cDNA for novel serine **protease** BSSP6 from human and mice, and immunoassay of BSSP6 for diagnosis)
IT **Antitumor agents**
Molecular cloning
Mouse
(cloning of cDNA for novel serine **protease** BSSP6 from human and mice, and immunoassay of BSSP6 for diagnosis)
IT Antibodies
RL: ARG (Analytical reagent use); BPN (Biosynthetic preparation); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)
(cloning of cDNA for novel serine **protease** BSSP6 from human and mice, and immunoassay of BSSP6 for diagnosis)
IT Alzheimer's disease
Epilepsy
Sterility
(diagnosis and treatment of; cloning of cDNA for novel serine **protease** BSSP6 from human and mice, and immunoassay of BSSP6 for diagnosis)
IT Inflammation
(diagnosis of; cloning of cDNA for novel serine **protease** BSSP6 from human and mice, and immunoassay of BSSP6 for diagnosis)
IT cDNA sequences
(for novel serine **protease** BSSP6 from human and mice)
IT Diagnosis
(immunodiagnosis; cloning of cDNA for novel serine **protease** BSSP6 from human and mice, and immunoassay of BSSP6 for diagnosis)
IT **Antibodies**
RL: ARG (Analytical reagent use); BPN (Biosynthetic preparation); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**monoclonal**; cloning of cDNA for novel serine **protease** BSSP6 from human and mice, and immunoassay of BSSP6 for diagnosis)
IT Prostate gland
(neoplasm, diagnosis and treatment of; cloning of cDNA for novel serine **protease** BSSP6 from human and mice, and immunoassay of BSSP6 for diagnosis)
IT Immunoassay
(of BSSP6; cloning of cDNA for novel serine **protease** BSSP6 from human and mice, and immunoassay of BSSP6 for diagnosis)
IT Protein sequences
(of novel serine **protease** BSSP6 from human and mice)
IT Pancreas, disease
(pancreatitis, diagnosis and treatment of; cloning of cDNA for novel serine **protease** BSSP6 from human and mice, and immunoassay of BSSP6 for diagnosis)
IT Animal
(transgenic; BSSP6 expression in; cloning of cDNA for novel serine **protease** BSSP6 from human and mice, and immunoassay of BSSP6 for diagnosis)
IT 37259-58-8P, Serine **Protease**
RL: ANT (Analyte); BPN (Biosynthetic preparation); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)
(BSSP6; cloning of cDNA for novel serine **protease** BSSP6 from human and mice, and immunoassay of BSSP6 for diagnosis)
IT 236739-16-5P 272763-27-6P, **Proteinase** serine, BSSP6 (human

brain) 272763-30-1P, **Proteinase** BSSP6 (mouse brain precursor)
272763-31-2P, **Proteinase**, serine BSSP6 (mouse brain)
272763-34-5P 272763-35-6P
RL: ANT (Analyte); BPN (Biosynthetic preparation); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)
(amino acid sequence; cloning of cDNA for novel serine **protease** BSSP6 from human and mice, and immunoassay of BSSP6 for diagnosis)

IT 272428-89-4 272763-26-5 272763-28-7 272763-29-8 272763-32-3
272763-33-4
RL: BPR (Biological process); PRP (Properties); BIOL (Biological study); PROC (Process)
(nucleotide sequence; cloning of cDNA for novel serine **protease** BSSP6 from human and mice, and immunoassay of BSSP6 for diagnosis)

IT 272103-63-6, 3: PN: WO0031284 SEQID: 3 unclaimed DNA 272103-66-9, 6: PN: WO0031284 SEQID: 6 unclaimed DNA 272103-67-0, 7: PN: WO0031284 SEQID: 7 unclaimed DNA 272103-70-5 272103-71-6 272103-72-7 272103-73-8
272765-71-6 272765-72-7 272765-87-4 272765-92-1 272765-93-2
272765-94-3 272765-95-4 272765-96-5 272765-97-6 272765-98-7
272765-99-8 272766-00-4 272766-01-5 272766-02-6 272766-03-7
272766-04-8 272766-05-9 272766-06-0 272766-07-1 272766-08-2
272766-09-3
RL: PRP (Properties)
(unclaimed nucleotide sequence; cloning of cDNA for novel serine **protease** BSSP6 from human and mice, and immunoassay of BSSP6 for diagnosis)

REFERENCE COUNT: 11
REFERENCE(S):
(2) Genset; WO 9931236 A2 1999 CAPLUS
(4) Human Genome Sci Inc; WO 9854963 A2 1998 CAPLUS
(5) Incyte Pharmaceuticals Inc; US 5840871 A CAPLUS
(6) Incyte Pharmaceuticals Inc; AU 9860419 A CAPLUS
(7) Incyte Pharmaceuticals Inc; WO 9832865 A1 1998 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 11 OF 18 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:277810 CAPLUS
DOCUMENT NUMBER: 132:326056
TITLE: Systems for oral delivery
INVENTOR(S): Russell-Jones, Gregory John
PATENT ASSIGNEE(S): Biotech Australia Pty. Ltd., Australia
SOURCE: PCT Int. Appl., 32 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000022909	A2	20000427	WO 1999-IB1872	19991018
WO 2000022909	A3	20001123		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 2000010712	A5	20000508	AU 2000-10712	19991018

PRIORITY APPLN. INFO.: US 1998-104827 P 19981019

WO 1999-IB1872 W 19991018

AB A pharmaceutical and a biol. active substance, for oral administration, can be "coated" or "encapsulated" with a carboxylic acid, such that the substance is protected from proteolysis in the stomach and is taken up from the intestine. It is thought that the carboxylic acids coat and protect the active agent from the proteolytic environment of the stomach, allowing the agent to pass safely through the stomach and to be absorbed in the small intestines. The carboxylic acid agent complex can be adopted for oral, nasal, buccal, and transdermal delivery of moderately sol. and even insol. bioactive agents.

ICI A61

CC 63-6 (Pharmaceuticals)

IT Adrenoceptor agonists
Allergy inhibitors
Analgesics
Anthelmintics
Anti-inflammatory agents
Antiarrhythmics
Antibiotics
Anticoagulants
Anticonvulsants
Antidepressants
Antidiabetic agents
Antihistamines
Antihypertensives
Antiparkinsonian agents
Antipsychotics
Antitumor agents
Antitussives
Antiviral agents
Anxiolytics
Appetite depressants
Blood products
Cholinergic agonists
Diuretics
Dopamine agonists
Expectorants
Fungicides
Hemostatics
Hypnotics and Sedatives
Imaging agents
Immunosuppressants
Inotropics
Muscarinic antagonists
Muscle relaxants
Radiopharmaceuticals
Thyroid gland
Tranquilizers
Vasodilators
Wound healing promoters
(carboxylic acids for encapsulating or enteric coating biol. active **agents** for delivery to intestine)

IT Angiogenic factors
CTLA-4 (antigen)
Carboxylic acids, biological studies
Chemotactic factors
Ciliary neurotrophic factor
Corticosteroids, biological studies
Eotaxin
Erythropoietin receptors
Hepatocyte growth factor
Insulin-like growth factor receptors
Interferons

Interleukin 10
Interleukin 11
Interleukin 12
Interleukin 13
Interleukin 15
Interleukin 16
Interleukin 17
Interleukin 18
Interleukin 1.alpha.
Interleukin 1.beta.
Interleukin 2
Interleukin 3
Interleukin 4
Interleukin 5
Interleukin 6
Interleukin 7
Interleukin 8
Interleukin 9
Lactoferrins
Lymphotoxin
Macrophage inflammatory protein 1.alpha.
Macrophage inflammatory protein 1.beta.
Macrophage inflammatory protein 2
Macrophage migration inhibitory factor
Midkines
Monocyte chemoattractant protein-1
Neuropeptides
Platelet-derived growth factors
Pleiotrophins
Prostaglandins
RANTES (chemokine)
Sex hormones
Stem cell factor
Steroids, biological studies
Tumor necrosis factors
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(carboxylic acids for encapsulating or enteric coating biol. active agents for delivery to intestine)

IT **Antibodies**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**monoclonal**; carboxylic acids for encapsulating or enteric coating biol. active agents for delivery to intestine)

IT 50-02-2 50-33-9, Phenylbutazone, biological studies 50-56-6, Oxytocin, biological studies 53-86-1, Indomethacin 57-10-3, Hexadecanoic acid, biological studies 57-11-4, Octadecanoic acid, biological studies 60-33-3, Linoleic acid, biological studies 76-93-7, Benzilic acid, biological studies 83-49-8, Hyodeoxycholic acid 85-01-8, Phenanthrene, biological studies 91-20-3, Naphthalene, biological studies 92-13-7, Pilocarpine 92-92-2, 4-Biphenylcarboxylic acid 98-73-7, 4-tert-Butylbenzoic acid 106-14-9, 12-Hydroxystearic acid 112-37-8, Undecanoic acid 112-38-9, Undecylenic acid 112-79-8, Elaidic acid 112-80-1, Oleic acid, biological studies 123-76-2, Levulinic acid 126-07-8, Griseofulvin 127-27-5, Pimaric acid 128-13-2, Ursodeoxycholic acid 129-20-4, Oxyphenbutazone 130-15-4, 1,4-Naphthalenedione 141-22-0, Ricinoleic acid 143-07-7, Dodecanoic acid, biological studies 302-79-4, Retinoic acid 303-98-0, Ubidecarenone 334-48-5, Decanoic acid 373-49-9, Palmitoleic acid 459-67-6, Hydnocarpic acid 463-40-1, Linolenic acid 474-25-9, Chenodeoxycholic acid 503-07-1, Vernolic acid 506-25-2, Isanic acid 506-26-3, .gamma.-Linolenic acid 506-30-9, Eicosanoic acid 506-32-1, Arachidonic acid 514-10-3, Abietic acid 524-42-5, 1,2-Naphthalenedione 525-66-6, Propranolol 530-78-9, Flufenamic acid 544-63-8, Tetradecanoic acid, biological studies 544-64-9, Myristoleic acid

611-95-0, 4-Benzoylbenzoic acid 621-82-9, Cinnamic acid, biological studies 641-81-6, Apocholic acid 646-30-0, Nonadecanoic acid 693-72-1, Vaccenic acid 1142-39-8, 4-Hexyloxybenzoic acid 1406-18-4, Vitamin E 2168-75-4, Ethyl 3,5-diacetamido-2,4,6-triiodobenzoate 2270-20-4, 5-Phenylvaleric acid 2430-94-6, cis-5-Dodecenoic acid 2493-84-7 2608-24-4, Piposulfan 2777-65-3, 10-Undecynoic acid 2984-55-6, 2-Hydroxydodecanoic acid 3115-49-9, (p-Nonylphenoxy)acetic acid 3575-31-3, 4-Octylbenzoic acid 4419-39-0, Beclomethasone 4521-28-2, 4-(4-Methoxyphenyl)-butyric acid 5104-49-4, Flurbiprofen 5451-55-8, 4-tert-Butylcyclohexanecarboxylic acid 5728-52-9, 4-Biphenylacetic acid 5731-13-5 6402-36-4, Traumatic acid 6950-82-9, 7-Hydroxycoumarin-4-acetic acid 6990-06-3, Fusidic acid 7689-03-4, Camptothecin 8001-27-2, Hirudin 9001-12-1, MMP-1 9001-27-8, Factor VIII 9001-28-9, Factor IX 9002-64-6, Parathyroid hormone 9003-99-0, Myeloperoxidase 9004-10-8, Insulin, biological studies 9005-49-6, Heparin, biological studies 9007-12-9, Calcitonin 9014-00-0, Luciferase 9014-42-0, Thrombopoietin 9034-40-6D, LHRH, analogs 9041-92-3 9054-89-1, Superoxide dismutase 9061-61-4, Nerve growth factor 11000-17-2, Vasopressin 11096-26-7, Erythropoietin 13539-59-8, Azapropazone 13598-36-2D, Phosphonic acid, alkylidenebis-derivs. 15307-86-5, Diclofenac 15687-27-1, Ibuprofen 15872-42-1, 4-Heptyloxybenzoic acid 15872-43-2, 4-Nonyloxybenzoic acid 15872-44-3, 4-Undecyloxybenzoic acid 17230-88-5, Danazol 20651-71-2, 4-Butylbenzoic acid 21643-38-9, 4-Hexylbenzoic acid 22071-15-4, Ketoprofen 22204-53-1, Naproxen 23812-34-2 25167-62-8, Docosahexaenoic acid 25354-97-6, 2-Hexyldecanoic acid 25378-27-2, Eicosapentaenoic acid 26171-23-3, Tolmetin 26764-41-0, Eicosenoic acid 27070-56-0, Eicosatrienoic acid 29679-58-1, Fenoprofen 29973-91-9, 4-Benzyloxy-3-methoxyphenylacetic acid 30748-29-9, Feprazone 34645-84-6, Fenclofenac 36322-90-4, Piroxicam 38194-50-2, Sulindac 38289-29-1, trans-4-Pentylcyclohexanecarboxylic acid 38350-87-7, 4-Heptylbenzoic acid 51110-01-1, Somatostatin 53483-12-8 55837-18-8, Butibufen 58574-03-1, 4'-Hydroxy-4-biphenylcarboxylic acid 58957-92-9, Idarubicin 59865-13-3, Cyclosporin 62229-50-9, Epidermal growth factor 67763-96-6, Insulin-like growth factor I 67763-97-7, Insulin-like growth factor II 74397-12-9, Limaprost 79955-99-0, MMP-3 81627-83-0, Macrophage colony stimulating factor 83869-56-1, Granulocyte macrophage colony stimulating factor 85637-73-6, Atriopeptin 105844-41-5, Plasminogen activator inhibitor 106096-92-8, Endothelial cell growth factors 106096-93-9, Fibroblast growth factor basic 106956-32-5, Oncostatin M 107000-34-0 113427-24-0 117147-70-3, Amphiregulin 120373-36-6, Unoprostone 121181-53-1, Filgrastim 122312-54-3, Epoetin beta 122320-05-2, Secretoryleukocyte **protease** inhibitor 123584-45-2, Fibroblast growth factor 4 123626-67-5, Endothelin-1 123774-72-1, Sargramostim 127464-60-2, Vascular endothelial growth factor 129653-64-1, Fibroblast growth factor 5 130939-41-2, Fibroblast growth factor 6 130939-66-1, Neurotrophin 3 139639-23-9, Tissue plasminogen activator 141256-52-2, MMP 7 143011-72-7, Granulocyte colony stimulating factor 143090-92-0, Anakinra 143375-33-1, Neurotrophin 4 146480-35-5, MMP 2 146480-36-6, MMP 9 148348-15-6, Fibroblast growth factor 7 151185-16-9, Fibroblast growth factor 9 155646-83-6, Heregulin-.beta.1 163150-12-7, Betacellulin 169494-85-3, Leptin 169592-56-7, Apopain 214210-48-7, Placenta growth factor 2 265112-35-4

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(carboxylic acids for encapsulating or enteric coating biol. active agents for delivery to intestine)

L25 ANSWER 12 OF 18 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:98300 CAPLUS
DOCUMENT NUMBER: 132:132356
TITLE: Chemically induced intracellular hyperthermia for therapeutic and diagnostic use

INVENTOR(S): Bachynsky, Nicholas; Roy, Woodie
PATENT ASSIGNEE(S): Texas Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 149 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000006143	A1	20000210	WO 1999-US16940	19990727
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9951318	A1	20000221	AU 1999-51318	19990727
EP 1098641	A1	20010516	EP 1999-935949	19990727
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.: US 1998-94286 P 19980727
WO 1999-US16940 W 19990727

AB Therapeutic pharmacol. agents and methods are disclosed for chem. induction of intracellular hyperthermia and/or free radicals for the diagnosis and treatment of infections, malignancy, and other medical conditions. A process and compn. are provided for the diagnosis or killing of cancer cells and inactivation of susceptible bacterial, parasitic, fungal, and viral pathogens by chem. generating heat, and/or free radicals and/or hyperthermia-inducible immunogenic determinants by using mitochondrial uncoupling agents, esp. 2,4-dinitrophenol, and their conjugates, either alone or in combination with other drugs, hormones, cytokines and radiation.

IC ICM A61K031-06
CC 1-12 (Pharmacology)
Section cross-reference(s): 9, 63

IT **Antitumor agents**
(adenocarcinoma; chem. induced intracellular hyperthermia for diagnostic and therapeutic use, and use with other **agents**)

IT Mammary gland
(**carcinoma**; chem. induced intracellular hyperthermia for diagnostic and therapeutic use, and use with other agents)

IT Alkylating agents, biological
Anti-infective agents
Anti-ischemic agents
Antibacterial agents
Antitumor agents
Antiviral agents
Combinatorial chemistry
Combinatorial library
Cyanine dyes
Diagnosis
Echinococcus multilocularis
Fungicides
Human immunodeficiency virus
Hyperthermia (therapeutic)
Infection
Lyme disease
Neoplasm

Parasiticides
Positron-emission tomography
Radiotherapy
Surgery
(chem. induced intracellular hyperthermia for diagnostic and therapeutic use, and use with other **agents**)

IT Cytokines
Histones
Interleukin 1
Interleukin 10
Interleukin 2
Interleukin 4
Leukotrienes
Nucleoside analogs
Oligosaccharides, biological studies
Polyenes
Polyethers, biological studies
Prostaglandins
Sulfonamides
Tetracyclines
Thromboxanes
Thyroid hormones
Tumor necrosis factors
Ubiquinones
Uncoupling protein
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(chem. induced intracellular hyperthermia for diagnostic and therapeutic use, and use with other agents)

IT neu (receptor)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**monoclonal** humanized **antibodies** to; chem. induced intracellular hyperthermia for diagnostic and therapeutic use, and use with other agents)

IT **Antibodies**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**monoclonal**, to HER-2/neu; chem. induced intracellular hyperthermia for diagnostic and therapeutic use, and use with other agents)

IT **Antitumor agents**
(prostate gland; chem. induced intracellular hyperthermia for diagnostic and therapeutic use, and use with other **agents**)

IT 9001-92-7, **Protease** 9039-48-9, Aromatase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; chem. induced intracellular hyperthermia for diagnostic and therapeutic use, and use with other agents)

REFERENCE COUNT: 3
REFERENCE(S): (1) Gordon; US 4569836 A 1986 CAPLUS
(2) Gordon; US 5622686 A 1997
(3) Rubin; US 5005588 A 1991

L25 ANSWER 13 OF 18 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:15354 CAPLUS
DOCUMENT NUMBER: 132:74546
TITLE: Relation of the TMPRSS2 gene to human cancers, methods for the diagnosis and treatment of said cancers, and drug screening assays
INVENTOR(S): Wong, Alexander K. C.; Tavtigian, Sean V.; Teng, David H. F.
PATENT ASSIGNEE(S): Myriad Genetics, Inc., USA
SOURCE: PCT Int. Appl., 89 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000000605	A1	20000106	WO 1999-US14622	19990629
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9948399	A1	20000117	AU 1999-48399	19990629
US 6166194	A	20001226	US 1999-342749	19990629

PRIORITY APPLN. INFO.: US 1998-91044 P 19980629
WO 1999-US14622 W 19990629

AB The invention provides protein and cDNA sequences of the TMPRSS2 gene and the tumor suppressor which it encodes. The invention is directed to the relation of the TMPRSS2 gene to human cancers and to methods for the diagnosis and prognosis of human cancer. A panel of 186 tumor cell lines was examd. for homozygous deletion of the TMPRSS2 gene, with BxPC3 being the sole cell line which contained such a deletion. The gene was also sequenced for 64 of these cell lines and the sequence was detd. to differ at five nucleotides from the previously reported sequence (Genbank U75329). The invention also relates to the therapy of human cancers which have a mutation in the TMPRSS2 gene, including gene therapy, protein replacement therapy and protein mimetics. Finally, the invention relates to the screening of drugs for cancer therapy.

IC ICM C12N015-11
ICS C12N015-63; C12P019-34; C12Q001-68; A01N037-18; A61K049-00

CC 3-3 (Biochemical Genetics)
Section cross-reference(s): 1, 6, 13

ST cDNA sequence human TMPRSS2 gene **tumor** suppressor; diagnosis therapy drug screening cancer

IT Immunoassay
(immunoblotting, use in detection of mutated TMPRSS2 gene **tumor** suppressor; relation of the TMPRSS2 gene to human cancers, methods for the diagnosis and treatment of said cancers, and drug screening assays)

IT Immunoassay
(immunocytochem., use in detection of mutated TMPRSS2 gene **tumor** suppressor; relation of the TMPRSS2 gene to human cancers, methods for the diagnosis and treatment of said cancers, and drug screening assays)

IT **Antibodies**
RL: ARG (Analytical reagent use); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(**monoclonal**, use in detection of mutated TMPRSS2 gene **tumor** suppressor; relation of the TMPRSS2 gene to human cancers, methods for the diagnosis and treatment of said cancers, and drug screening assays)

IT **Antitumor agents**
Drug screening
Gene therapy
Molecular cloning
Pancreas, neoplasm
(relation of the TMPRSS2 gene to human cancers, methods for the diagnosis and treatment of said cancers, and drug screening assays)

IT Gene, animal

RL: ARU (Analytical role, unclassified); BOC (Biological occurrence); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(**tumor** suppressor, TMPRSS2; relation of the TMPRSS2 gene to human cancers, methods for the diagnosis and treatment of said cancers, and drug screening assays)

IT 9001-92-7, **Protease**
RL: ARG (Analytical reagent use); BAC (Biological activity or effector, except adverse); CAT (Catalyst use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(use in drug screening assay; relation of the TMPRSS2 gene to human cancers, methods for the diagnosis and treatment of said cancers, and drug screening assays)

REFERENCE COUNT: 3
REFERENCE(S):
(1) Donahue; US 5359047 A 1994 CAPLUS
(2) Paoloni-Giacobino; Genomics 1997, V44, P309 CAPLUS
(3) Skolnick; US 5710001 A 1998 CAPLUS

L25 ANSWER 14 OF 18 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:784132 CAPLUS
DOCUMENT NUMBER: 132:34754
TITLE: Novel **tumor** antigen useful in diagnosis and therapy of prostate and colon cancer
INVENTOR(S): Afar, Daniel E.; Hubert, Rene S.; Leong, Kahan; Raitano, Arthur B.; Saffran, Douglas C.
PATENT ASSIGNEE(S): Urogenesys, Inc., USA
SOURCE: PCT Int. Appl., 58 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9962942	A2	19991209	WO 1999-US12253	19990601
W: AT, AT, AU, BR, CA, CH, CN, DE, DE, DK, DK, ES, FI, FI, GB, IL, JP, KR, MX, NO, NZ, RU, SE, SG, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9944136	A1	19991220	AU 1999-44136	19990601
EP 1082341	A2	20010314	EP 1999-927164	19990601
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.:
US 1998-87598 P 19980601
US 1998-91474 P 19980629
US 1999-129521 P 19990414
WO 1999-US12253 W 19990601

AB Compns. for the diagnosis and therapy of prostate and colon cancer, derived from or based on a novel prostate-specific, androgen-regulated, cell surface serine protease termed 20P1F12/TMPRSS2 are described. A full length cDNA comprising the entire coding sequence of the 20P1F12/TMPRSS2 gene (also designated 20P1F12-GTC1) is provided. Among the compns. provided are antibodies that bind to 20P1F12/TMPRSS2 proteins and polypeptide fragments thereof, including antibodies labeled with a detectable marker or toxin or therapeutic compn. Several monoclonal antibodies specifically reactive with 20P1F12/TMPRSS2 are also described herein.

IC ICM C07K014-00
CC 15-2 (Immunochemistry)
Section cross-reference(s): 3
ST TMPRSS2 20P1F12 gene protein prostate cancer; colon cancer 20P1F12 TMPRSS2 protein antibody; sequence serine **protease** TMPRSS2 cDNA human

IT Plasmid vectors
(20P1F12-GTC1; **tumor** antigen 20P1F12/TMPRSS2 useful in diagnosis and therapy of prostate and colon cancer)
IT Gene, animal
RL: BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(20P1F12/TMPRSS2; **tumor** antigen 20P1F12/TMPRSS2 useful in diagnosis and therapy of prostate and colon cancer)
IT PCR (polymerase chain reaction)
(RT-PCR (reverse transcription-PCR), assay for **tumor** marker by; **tumor** antigen 20P1F12/TMPRSS2 useful in diagnosis and therapy of prostate and colon cancer)
IT Nucleic acid hybridization
(assay for **tumor** marker by; **tumor** antigen 20P1F12/TMPRSS2 useful in diagnosis and therapy of prostate and colon cancer)
IT Diagnosis
(cancer; **tumor** antigen 20P1F12/TMPRSS2 useful in diagnosis and therapy of prostate and colon cancer)
IT Intestine, neoplasm
(colon, inhibitors; **tumor** antigen 20P1F12/TMPRSS2 useful in diagnosis and therapy of prostate and colon cancer)
IT **Antitumor agents**
Intestine, neoplasm
(colon; **tumor** antigen 20P1F12/TMPRSS2 useful in diagnosis and therapy of prostate and colon cancer)
IT Drugs
(conjugate; **tumor** antigen 20P1F12/TMPRSS2 useful in diagnosis and therapy of prostate and colon cancer)
IT Toxins
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(conjugates; **tumor** antigen 20P1F12/TMPRSS2 useful in diagnosis and therapy of prostate and colon cancer)
IT Neoplasm
(diagnosis; **tumor** antigen 20P1F12/TMPRSS2 useful in diagnosis and therapy of prostate and colon cancer)
IT **Antibodies**
RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**monoclonal**; **tumor** antigen 20P1F12/TMPRSS2 useful in diagnosis and therapy of prostate and colon cancer)
IT Prostate gland
(neoplasm, inhibitors; **tumor** antigen 20P1F12/TMPRSS2 useful in diagnosis and therapy of prostate and colon cancer)
IT Prostate gland
(neoplasm; **tumor** antigen 20P1F12/TMPRSS2 useful in diagnosis and therapy of prostate and colon cancer)
IT **Antitumor agents**
(prostate gland; **tumor** antigen 20P1F12/TMPRSS2 useful in diagnosis and therapy of prostate and colon cancer)
IT Androgens
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(regulated; **tumor** antigen 20P1F12/TMPRSS2 useful in diagnosis and therapy of prostate and colon cancer)
IT Labels
Molecular cloning
Protein sequences
Tumor markers
cDNA sequences
(**tumor** antigen 20P1F12/TMPRSS2 useful in diagnosis and therapy of prostate and colon cancer)
IT Antibodies

RL: BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**tumor** antigen 20P1F12/TMPRSS2 useful in diagnosis and therapy of prostate and colon cancer)

IT Antisense DNA
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**tumor** antigen 20P1F12/TMPRSS2 useful in diagnosis and therapy of prostate and colon cancer)

IT Probes (nucleic acid)
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**tumor** antigen 20P1F12/TMPRSS2 useful in diagnosis and therapy of prostate and colon cancer)

IT Antigens
RL: BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**tumor**-assocd., 20P1F12/TMPRSS2; **tumor** antigen 20P1F12/TMPRSS2 useful in diagnosis and therapy of prostate and colon cancer)

IT 251951-41-4
RL: BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(amino acid sequence; **tumor** antigen 20P1F12/TMPRSS2 useful in diagnosis and therapy of prostate and colon cancer)

IT 197982-63-1 198056-06-3
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(nucleotide sequence; **tumor** antigen 20P1F12/TMPRSS2 useful in diagnosis and therapy of prostate and colon cancer)

IT 251985-42-9
RL: BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nucleotide sequence; **tumor** antigen 20P1F12/TMPRSS2 useful in diagnosis and therapy of prostate and colon cancer)

IT 252212-87-6, Serine **protease** 20P1F12/TMPRSS2
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**tumor** antigen 20P1F12/TMPRSS2 useful in diagnosis and therapy of prostate and colon cancer)

IT 250353-44-7 252020-77-2
RL: PRP (Properties)
(unclaimed nucleotide sequence; novel **tumor** antigen useful in diagnosis and therapy of prostate and colon cancer)

IT 181316-81-4 186074-35-1, PN: JP11276170 PAGE:4 unclaimed DNA 193427-77-9 250296-39-0 250353-70-9 252020-74-9 252020-75-0 252020-76-1
RL: PRP (Properties)
(unclaimed sequence; novel **tumor** antigen useful in diagnosis and therapy of prostate and colon cancer)

L25 ANSWER 15 OF 18 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:139991 CAPLUS
DOCUMENT NUMBER: 130:193957
TITLE: Methods for using granzymes and their binding molecules for diagnosing and treating diseases characterized by abnormal apoptosis
INVENTOR(S): Lieberman, Judy; Beresford, Paul J.
PATENT ASSIGNEE(S): Center for Blood Research, Inc., USA
SOURCE: PCT Int. Appl., 56 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9909206	A1	19990225	WO 1998-US17022	19980817
W: CA, JP				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 1007723	A1	20000614	EP 1998-942081	19980817
R: DE, FR, GB				

PRIORITY APPLN. INFO.: US 1997-56333 P 19970818
WO 1998-US17022 W 19980817

AB A method for detg. if an animal is at risk for a disease resulting in abnormal apoptosis is described. An animal is provided and an aspect of metab. or structure of a serine protease, e.g., a granzyme, or a serine protease binding mol. in the animal is evaluated. An abnormality in the aspect of the metab. or structure is diagnostic of being at risk for a disease resulting in abnormal apoptosis. Also described are methods for evaluating an agent for use in modulating apoptosis, methods for effecting or inhibiting apoptosis in a cell, and methods for treating unwanted cell or infectious particle proliferation or treating an autoimmune disease or a transplant graft rejection in an animal. Pharmaceutical compns. are also provided. Examples describe prodn. of active and inactive recombinant human granzyme A in Escherichia coli, prodn. of monoclonal and polyclonal antibodies to human granzyme A, substrate recognition and enzyme kinetics of rGranA, etc.

IC ICM C12Q001-02
ICS C12N001-38; A61K038-10

CC 9-2 (Biochemical Methods)
Section cross-reference(s): 1, 3, 7, 14, 15, 63

ST granzyme A diagnosis treatment abnormal apoptosis; serine **protease** abnormal apoptosis diagnosis treatment

IT Genes (animal)
RL: BPR (Biological process); BUU (Biological use, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(encoding serine **protease**, etc.; methods using granzymes and their binding mols. for diagnosing and treating diseases characterized by abnormal apoptosis)

IT **Antitumor agents**
Apoptosis
Diagnosis
Diseases (animal)
Drug screening
Gene therapy
Immunoblotting
Immunoprecipitation
(methods using granzymes and their binding mols. for diagnosing and treating diseases characterized by abnormal apoptosis)

IT Metabolism
(of serine **protease** or binding mol., evaluation of; methods using granzymes and their binding mols. for diagnosing and treating diseases characterized by abnormal apoptosis)

IT Molecules
(serine **protease**- or granzyme-binding; methods using granzymes and their binding mols. for diagnosing and treating diseases characterized by abnormal apoptosis)

IT Antibodies
Monoclonal antibodies
RL: BPN (Biosynthetic preparation); BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(to granzyme A, etc.; methods using granzymes and their binding mols. for diagnosing and treating diseases characterized by abnormal apoptosis)

IT Autoimmune diseases

Bacterial infection
Infection
Lymphoproliferative disorders
Transplant rejection
Tumors (animal)
Viral infection
(treatment of; methods using granzymes and their binding mols. for diagnosing and treating diseases characterized by abnormal apoptosis)

IT 9003-98-9, DNase 9003-98-9D, DNase, complexes with binding mol. for serine **protease**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(for effecting apoptosis in deficient cells; methods using granzymes and their binding mols. for diagnosing and treating diseases characterized by abnormal apoptosis)

IT 37259-58-8, Serine **protease** 106178-18-1, Granzyme
RL: ANT (Analyte); BAC (Biological activity or effector, except adverse); BPR (Biological process); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)
(methods using granzymes and their binding mols. for diagnosing and treating diseases characterized by abnormal apoptosis)

REFERENCE COUNT: 7
REFERENCE(S):
(1) Beresford, P; Proc Natl Acad Sci USA 1997, V94, P9285 CAPLUS
(2) Pasternack; US 5017489 A 1991 CAPLUS
(3) Shi, L; J Exp Med 1992, V175, P553 CAPLUS
(4) Smyth, M; Clin Exp Pharm Phys 1994, V21, P67 CAPLUS
(5) Sower, L; J Immunol 1996, V156, P2585 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 16 OF 18 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:136795 CAPLUS
DOCUMENT NUMBER: 130:191886
TITLE: Stimulation, modulation and/or inhibition of endothelial **proteolytic** activity and/or angiogenic activity
INVENTOR(S): Pepper, Michael S.; Alitalo, Kari; Eriksson, Ulf
PATENT ASSIGNEE(S): Ludwig Institute for Cancer Research, USA; Helsinki University Licensing Ltd., Oy; University of Geneva
SOURCE: PCT Int. Appl., 51 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9908522	A1	19990225	WO 1998-US16816	19980814
W: AU, CA, CN, JP, KR, NZ				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9889056	A1	19990308	AU 1998-89056	19980814
EP 1011328	A1	20000628	EP 1998-940875	19980814
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2001514867	T2	20010918	JP 2000-509282	19980814

PRIORITY APPLN. INFO.: US 1997-55868 P 19970815
WO 1998-US16816 W 19980814

AB Vascular endothelial growth factor-B (VEGF-B) and vascular endothelial growth factor-C (VEGF-C) are angiogenic polypeptides. It has been shown that VEGF-B and -C are angiogenic in vitro esp. in combination with bFGF.

VEGF-C also increases plasminogen activator (PA) activity in bovine endothelial cell lines and this is accompanied by a concomitant increase in PA inhibitor-1. Addn. of .alpha.2-antiplasmin to bovine endothelial cells co-treated with bFGF and VEGF-C partially inhibits collagen gel invasion.

IC ICM A01N037-18
ICS A01N043-04; C07H021-04; C12N005-00; C12N005-09; C12N005-10; C12N015-09; C12N015-12; C12Q001-68

CC 1-8 (Pharmacology)

IT Nucleic acids
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antisense; stimulation, modulation and/or inhibition of endothelial **proteolytic** activity and/or angiogenic activity)

IT Artery endothelium
(aortic; stimulation, modulation and/or inhibition of endothelial **proteolytic** activity and/or angiogenic activity)

IT Cattle
(bovine endothelial cell; stimulation, modulation and/or inhibition of endothelial **proteolytic** activity and/or angiogenic activity)

IT Genes
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(cytokine-encoding; stimulation, modulation and/or inhibition of endothelial **proteolytic** activity and/or angiogenic activity)

IT Aorta
Lymphatic vessel
(endothelium; stimulation, modulation and/or inhibition of endothelial **proteolytic** activity and/or angiogenic activity)

IT Collagens, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(invasion; stimulation, modulation and/or inhibition of endothelial **proteolytic** activity and/or angiogenic activity)

IT Vascular endothelium
(lymph vessel; stimulation, modulation and/or inhibition of endothelial **proteolytic** activity and/or angiogenic activity)

IT Urokinase-type plasminogen activator receptors
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(mRNA; stimulation, modulation and/or inhibition of endothelial **proteolytic** activity and/or angiogenic activity)

IT **Antitumor agents**
(solid **tumor**; stimulation, modulation and/or inhibition of endothelial **proteolytic** activity and/or angiogenic activity)

IT Angiogenesis
Angiogenesis inhibitors
Metastasis inhibitors
Protein degradation
Vascular endothelium
(stimulation, modulation and/or inhibition of endothelial **proteolytic** activity and/or angiogenic activity)

IT Cytokines
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(stimulation, modulation and/or inhibition of endothelial **proteolytic** activity and/or angiogenic activity)

IT Neutralizing antibodies
Neutralizing **monoclonal antibodies**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(to angiogenic cytokines; stimulation, modulation and/or inhibition of endothelial **proteolytic** activity and/or angiogenic activity)

IT 139639-23-9, Tissue plasminogen activator 139639-24-0, Urokinase plasminogen activator
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)

(mRNA; stimulation, modulation and/or inhibition of endothelial **proteolytic** activity and/or angiogenic activity)

IT 62031-54-3, Fibroblast growth factor 105913-11-9, Plasminogen activator 106096-93-9, Basic fibroblast growth factor 127464-60-2, Vascular endothelial growth factor 140208-23-7, Plasminogen activator inhibitor-1 188417-84-7, Vascular endothelial growth factor C 192662-83-2, Vascular endothelial growth factor B
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(stimulation, modulation and/or inhibition of endothelial **proteolytic** activity and/or angiogenic activity)

IT 9049-68-7, Antiplasmin 138757-15-0, .alpha.2-Antiplasmin
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stimulation, modulation and/or inhibition of endothelial **proteolytic** activity and/or angiogenic activity)

REFERENCE COUNT: 6
REFERENCE(S):
(1) Battegay, E; Journal of Molecular Medicine 1995, V73(7), P333 CAPLUS
(2) Enholm, B; Oncogene 1997, V14, P2475 CAPLUS
(3) Hu, G; Proceedings of the National Academy of Sciences 1994, V91, P12096 CAPLUS
(4) Koolwijk, P; The Journal of Cell biology 1996, V132(6), P1177 CAPLUS
(5) Pepper, M; Biochemical and Biophysical Research Communications 1992, V189(2), P824 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 17 OF 18 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:766507 CAPLUS
DOCUMENT NUMBER: 130:29221
TITLE: Preparation of solid porous matrixes for pharmaceutical uses
INVENTOR(S): Unger, Evan C.
PATENT ASSIGNEE(S): Imarx Pharmaceutical Corp., USA
SOURCE: PCT Int. Appl., 139 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9851282	A1	19981119	WO 1998-US9570	19980512
W: AU, BR, CA, CN, JP, KR, NZ				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9873787	A1	19981208	AU 1998-73787	19980512
EP 983060	A1	20000308	EP 1998-921109	19980512
R: DE, FR, GB, IT, NL				
US 2001018072	A1	20010830	US 2001-828762	20010409

PRIORITY APPLN. INFO.:
US 1997-46379 P 19970513
US 1998-75477 A 19980511
WO 1998-US9570 W 19980512

AB A solid porous matrix formed from a surfactant, a solvent, and a bioactive agent is described. Thus, amphotericin nanoparticles were prepd. by using ZrO2 beads and a surfactant. The mixt. was milled for 24 h.

IC ICM A61K009-10
CC 63-6 (Pharmaceuticals)
IT Allergy inhibitors
Anesthetics
Angiotensin-converting enzyme inhibitors

Anti-inflammatory drugs
Antianginal agents
Antibiotics
Anticoagulants
Antirheumatic drugs
Antitumor agents
Antiviral agents
Blood products
Coryneform bacteria
Diabetic retinopathy
Drug delivery systems
Fungicides
Hypnotics and Sedatives
Microparticles (drug delivery systems)
Mycobacterium
Nanoparticles (drug delivery systems)
Narcotics
Neuromuscular blocking agents
Nonionic surfactants
Preservatives
Protozoacides
Tuberculostatics
.beta.-Lactam antibiotics
(prepn. of solid porous matrixes for pharmaceutical uses)

IT **Monoclonal antibodies**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of solid porous matrixes for pharmaceutical uses)

IT **Tumor** necrosis factors
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of solid porous matrixes for pharmaceutical uses)

IT 9001-92-7, **Protease**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(receptors; prepn. of solid porous matrixes for pharmaceutical uses)

REFERENCE COUNT: 1
REFERENCE(S): (1) Wong; US 5569448 A 1996 CAPLUS

L25 ANSWER 18 OF 18 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:26256 CAPLUS
DOCUMENT NUMBER: 126:42676
TITLE: Use of extracellular cysteine **protease** to inhibit cell proliferation
INVENTOR(S): Musser, James M.; Kapur, Vivek; Ananthaswamy, Honnavara N.; Fernandez, Antonio
PATENT ASSIGNEE(S): Baylor College of Medicine, USA; Board of Regents, the University of Texas System
SOURCE: PCT Int. Appl., 99 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9634941	A1	19961107	WO 1996-US5997	19960430
W: AU, CA, JP				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5776747	A	19980707	US 1995-447778	19950523
AU 9657188	A1	19961121	AU 1996-57188	19960430
PRIORITY APPLN. INFO.:			US 1995-432692	19950501
			US 1994-279973	19940720
			WO 1996-US5997	19960430

AB Compns. comprising cysteine protease, for example, from streptococcal

species, find use in modulating growth of cells, in particular inhibition of cell proliferation, esp. tumor cells. Cell growth inhibition compns. may addnl. include an adjunctive agent. Methods for screening to identify tumor cells sensitive to the growth-modulating effects of the cysteine protease also are provided.

IC ICM C12N005-02
ICS C12N009-50; C12N009-52

CC 1-6 (Pharmacology)
Section cross-reference(s): 7, 15

ST cysteine **proteinase** antitumor cell proliferation sequence

IT Fibronectins
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(cleavage of; use of extracellular cysteine **protease** to inhibit cell proliferation)

IT **Monoclonal antibodies**
RL: BPN (Biosynthetic preparation); MFM (Metabolic formation); THU (Therapeutic use); BIOL (Biological study); FORM (Formation, nonpreparative); PREP (Preparation); USES (Uses)
(cysteine **protease**-specific; use of extracellular cysteine **protease** to inhibit cell proliferation)

IT Matrix proteins
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(extracellular, cleavage of; use of extracellular cysteine **protease** to inhibit cell proliferation)

IT Immunoassay
(for cysteine **protease** expression; use of extracellular cysteine **protease** to inhibit cell proliferation)

IT Vaccines
(intranasal; use of extracellular cysteine **protease** to inhibit cell proliferation)

IT Antigens
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(of bacterial cysteine **protease**; use of extracellular cysteine **protease** to inhibit cell proliferation)

IT Genes (microbial)
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); OCCU (Occurrence)
(speB, cysteine **protease** encoded by; use of extracellular cysteine **protease** to inhibit cell proliferation)

IT Heart
(**tumors**; use of extracellular cysteine **protease** to inhibit cell proliferation)

IT **Antitumor agents**
Brain **tumors**
Breast **tumors**
Carcinoma inhibitors
Drug delivery systems
Gastric **tumors**
Intestinal **tumors**
Leukemia inhibitors
Liver **tumors**
Lung **tumors**
Lymphoma inhibitors
Melanoma inhibitors
PCR (polymerase chain reaction)
Pancreatic **tumors**
Prostatic **tumors**
Sarcoma inhibitors
Skin **tumors**
Streptococcus pyogenes
(use of extracellular cysteine **protease** to inhibit cell proliferation)

IT Interleukin 1.beta.
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(use of extracellular cysteine **protease** to inhibit cell proliferation)

IT 130456-83-6
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(amino acid sequence; use of extracellular cysteine **protease** to inhibit cell proliferation)

IT 97599-20-7, Interleukin 1.beta. (human clone pIL-1-14 precursor reduced)
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(cleavage of; use of extracellular cysteine **protease** to inhibit cell proliferation)

IT 37353-41-6P, Cysteine **protease**
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation); USES (Uses)
(extracellular; use of extracellular cysteine **protease** to inhibit cell proliferation)

IT 122191-40-6, Interleukin 1.beta. convertase
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(use of extracellular cysteine **protease** to inhibit cell proliferation)

IT 177746-48-4 177746-49-5 177746-50-8 177746-51-9 177746-52-0
177746-53-1 177746-54-2 184777-98-8 184777-99-9
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use of extracellular cysteine **protease** to inhibit cell proliferation)

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=> d his

     (FILE 'MEDLINE' ENTERED AT 13:43:27 ON 22 OCT 2001)
                DEL HIS Y
L1         517849 S C4./CT (L) TH./CT
L2              0 S ANTIBODIES, MONOCLONAL+NT/CT (L) TU./CY
L3          10904 S ANTIBODIES, MONOCLONAL+NT/CT (L) TU./CT
L4           2890 S L1/MAJ AND L3
L5           2542 S IMMUNOTOXINS+NT/CT
L6           7436 S L5 OR CYTOTOXIN?
L7            441 S L4 AND L6
L8         601396 S HYDROLASES+NT/CT
L9              0 S L7 AND LL8
L10             8 S L7 AND L8
L11         13018 S CAPILLARY PERMEABILITY/CT
L12             3 S L11 AND L7
L13            90 S MH1 OR MH 1
L14             0 S L13 AND L7
L15             0 S L13 AND L4
L16             2 S L13 AND L1
L17         33375 S LIPOLYTIC OR  PROTEOLYTIC
L18             0 S L7 AND L17
L19             3 S L4 AND L17
L20            16 S L10 OR L12 OR L16 OR L19
L21             3 S L17 AND L4
L22         23098 S FIBRIN#
L23             0 S L7 AND L22
L24             0 S L4 AND L23
L25            16 S L21 OR L20
L26          3729 S TUMOR# (4A) (DAMAG? OR PERMEAB? OR MEMBRAN?)
L27             3 S L26 AND L7
L28            18 S L25 OR L27

=> d .med 1-18

L28  ANSWER 1 OF 18     MEDLINE
AN   2001334091     MEDLINE
DN   21295012   PubMed ID: 11401781
TI   Bioimmunotherapeutic targets on angiogenetic blood vessels in solid
     malignangies.
AU   Maio M; Altomonte M; Calabro L; Fonsatti E
CS   Cancer Bioimmunotherapy Unit, Centro di Riferimento Oncologico, Istituto
     Nazionale di Ricovero e Cura a Carattere Scientifico, 33081 Aviano,
     Italy.. mmaio@cro.it
SO   FRONTIERS IN BIOSCIENCE, (2001 Jun 1) 6 D776-84.  Ref: 109
     Journal code: CUE; 9702166. ISSN: 1093-4715.
CY   United States
DT   Journal; Article; (JOURNAL ARTICLE)
     General Review; (REVIEW)
     (REVIEW LITERATURE)
LA   English
FS   Priority Journals
EM   200110
ED   Entered STN: 20011015
     Last Updated on STN: 20011015
     Entered Medline: 20011011
AB   Physiological angiogenesis is a tightly regulated process that occurs
     mainly during reproduction, development and wound healing. Although
     angiogenesis is a continuous process, different consecutive steps can be
     identified, including: i) release of pro-angiogenetic factors; ii) release
     of proteolytic enzymes; iii) endothelial cell migration,
     morphogenesis and proliferation. Angiogenesis is also a hallmark of
     malignant diseases, and an inverse correlation between tumor vascularity
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and survival was demonstrated. Thus, strategies aimed at interfering with tumor blood supply by targeting tumor vasculature, presently represent promising new approaches for the treatment of solid malignancies. In fact, at least 30 angiogenetic inhibitors, utilized alone or in combination with other therapeutic agents, are currently being tested in clinical trials in humans. In this paper, we will review current knowledges on selected molecules expressed by endothelial cells and involved in distinct steps of the angiogenetic process, that represent potential targets for bioimmunotherapeutic approaches in human malignancies.

CT Check Tags: Human; Support, Non-U.S. Gov't
*Angiogenesis Inhibitors: TU, therapeutic use
***Antibodies, Monoclonal: TU, therapeutic use**
Antigens, CD31: IM, immunology
*Antineoplastic Agents: TU, therapeutic use
Collagen: TU, therapeutic use
Endothelial Growth Factors: AI, antagonists & inhibitors
Endothelial Growth Factors: IM, immunology
Lymphokines: AI, antagonists & inhibitors
Lymphokines: IM, immunology
Matrix Metalloproteinases: AI, antagonists & inhibitors
Neoplasms: BS, blood supply
***Neoplasms: TH, therapy**
Neovascularization, Pathologic
Peptide Fragments: TU, therapeutic use
Receptor Protein-Tyrosine Kinases: AI, antagonists & inhibitors
Receptor Protein-Tyrosine Kinases: IM, immunology
Receptors, Growth Factor: AI, antagonists & inhibitors
Receptors, Growth Factor: IM, immunology
Receptors, Vitronectin: AI, antagonists & inhibitors
Receptors, Vitronectin: IM, immunology
Vascular Cell Adhesion Molecule-1: IM, immunology

L28 ANSWER 2 OF 18 MEDLINE
AN 2001113533 MEDLINE
DN 21028957 PubMed ID: 11155818
TI Cell surface receptor-targeted therapy of acute myeloid leukemia: a review.
AU Frankel A E; Sievers E L; Scheinberg D A
CS Department of Cancer Biology, Wake Forest University School of Medicine, Medical Center Drive, Winston-Salem, NC 27157, USA.
SO CANCER BIOTHERAPY & RADIOPHARMACEUTICALS, (2000 Oct) 15 (5) 459-76. Ref: 84
Journal code: DLF. ISSN: 1084-9785.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200102
ED Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010215
AB Combination chemotherapy produces remissions in patients with acute myeloid leukemia (AML). However, the majority of patients ultimately relapse and die with cytotoxic drug resistant blasts. Novel agents which circumvent resistance are needed. One such class are AML-cell surface targeted proteins. These genetically engineered polypeptides are hybrid molecules composed of two moieties--a haptophore which triggers AML cell binding and a toxophore which kills the cell. The haptophore or ligand portion consists of a monoclonal antibody or antibody fragment or a cytokine. These peptides react with cell surface receptors or antigens on AML cells. The haptophore is genetically or chemically linked to the

toxophore. The toxophore may consist of an antibody Fc domain which triggers antibody-dependent cell cytotoxicity, a DNA-damaging cytotoxic drug, a radionuclide or a protein synthesis-inactivating peptide toxin. The toxophore may provide a cell death signal that overcomes standard resistance phenotypes. Further, the targeting provided by the haptophore may reduce normal tissue toxicities. This review describes some of the properties of the cell surface molecular targets, the reactive haptophores and toxophores and how these functional peptides have been optimally combined to kill leukemic blasts in patients with AML.

CT Check Tags: Animal; Human
Acute Disease
Antibiotics, Aminoglycoside: TU, therapeutic use
Antibodies, Monoclonal: IM, immunology
Antibodies, Monoclonal: ME, metabolism
***Antibodies, Monoclonal: TU, therapeutic use**
Antibody-Dependent Cell Cytotoxicity
*Antigens, CD: IM, immunology
Antigens, CD: ME, metabolism
Antigens, CD45: IM, immunology
*Antigens, Differentiation, Myelomonocytic: IM, immunology
Antigens, Differentiation, Myelomonocytic: ME, metabolism
*Antigens, Surface: IM, immunology
Antigens, Surface: ME, metabolism
*Antineoplastic Agents: TU, therapeutic use
Cell Death: IM, immunology
Clinical Trials
Hybridomas: IM, immunology
Hybridomas: ME, metabolism
IgG: IM, immunology
IgG: ME, metabolism
IgM: IM, immunology
IgM: ME, metabolism
***Immunotoxins: TU, therapeutic use**
Iodine Radioisotopes: TU, therapeutic use
Leukemia, Myeloid: IM, immunology
Leukemia, Myeloid: PA, pathology
***Leukemia, Myeloid: TH, therapy**
Ligands
Mice
Radioimmunotherapy: MT, methods
Tumor Stem Cells: PA, pathology

L28 ANSWER 3 OF 18 MEDLINE
AN 2000239226 MEDLINE
DN 20239226 PubMed ID: 10778955
TI A phase I study of combination therapy with immunotoxins IgG-HD37-deglycosylated ricin A chain (dgA) and IgG-RFB4-dgA (Combotox) in patients with refractory CD19(+), CD22(+) B cell lymphoma.
AU Messmann R A; Vitetta E S; Headlee D; Senderowicz A M; Figg W D; Schindler J; Michiel D F; Creekmore S; Steinberg S M; Kohler D; Jaffe E S; Stetler-Stevenson M; Chen H; Ghetie V; Sausville E A
CS Developmental Therapeutics Program, Clinical Trials Unit, Medicine Branch, National Cancer Institute, Bethesda, Maryland 20892-1906, USA.. messmann@pop.nci.nih.gov
NC FDR 001124-03 (FDA)
SO CLINICAL CANCER RESEARCH, (2000 Apr) 6 (4) 1302-13. Journal code: C2H; 9502500. ISSN: 1078-0432.
CY United States
DT (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE I)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals

EM 200008
ED Entered STN: 20000811
Last Updated on STN: 20000811
Entered Medline: 20000803

AB This study used an 8-day continuous infusion regimen of a 1:1 mixture of two immunotoxins (ITs) prepared from deglycosylated ricin A chain (dgA) conjugated to monoclonal antibodies directed against CD22 (RFB4-dgA) and CD19 (HD37-dgA; Combotox) in a Phase I trial involving 22 patients with refractory B cell lymphoma to determine the maximum tolerated dose, clinical pharmacology, and toxicity profile and to characterize any clinical responses. Adult patients received a continuous infusion of Combotox at 10, 20, or 30 mg/m2/192 h. No intrapatient dose escalation was permitted. Patients with > or =50 circulating tumor cells (CTCs)/mm3 in peripheral blood tolerated all doses without major toxicity. The maximum level of serum IT (Cmax) achieved in this group was 345 ng/ml of RFB4-dgA and 660 ng/ml of HD37-dgA (1005 ng/ml of Combotox). In contrast, patients without CTCs (<50/mm3) had unpredictable clinical courses that included two deaths probably related to the IT. Additionally, patients exhibited a significant potential for association between mortality and a history of either autologous bone marrow or peripheral blood stem cell transplants (P2 = 0.003) and between mortality and a history of radiation therapy (P2 = 0.036). In patients with CTCs, prior therapies appeared to have little impact on toxicity. Subsequent evaluation of the ITs revealed biochemical heterogeneity between two lots of HD37-dgA. In addition, HD37-dgA thawed at the study site tended to contain significant particulates, which were not apparent in matched controls stored at the originating site. This suggests that a tendency to aggregate may have resulted from shipping, storage, and handling of the IT that occurred prior to preparation for administration. It is not clear to what extent, if any, the aggregation of HD37-dgA IT was related to the encountered clinical toxicities; however, the potential to aggregate does suggest one possible basis for problems in our clinical experience with HD37-dgA and leads us to the conclusion that non-aggregate-forming formulations for these ITs should be pursued prior to future clinical trials.

CT Check Tags: Female; Human; Male; Support, U.S. Gov't, P.H.S.
Adult
Aged
Antibodies: BL, blood
Antibodies: DE, drug effects
Antibodies, Monoclonal: AE, adverse effects
*Antibodies, Monoclonal: PK, pharmacokinetics
Antibodies, Monoclonal: TU, therapeutic use
*Antigens, CD: IM, immunology
*Antigens, CD19: IM, immunology
*Antigens, Differentiation, B-Lymphocyte: IM, immunology
Area Under Curve
Capillary Permeability: DE, drug effects
Chromatography, High Pressure Liquid: MT, methods
Diarrhea: CI, chemically induced
Dose-Response Relationship, Drug
Drug Therapy, Combination
Fatigue: CI, chemically induced
Fever: CI, chemically induced
Immunotoxins: AE, adverse effects
***Immunotoxins: PK, pharmacokinetics**
Immunotoxins: TU, therapeutic use
Infusions, Intravenous
Lymphoma, B-Cell: IM, immunology
***Lymphoma, B-Cell: TH, therapy**
Metabolic Clearance Rate
Middle Age
Neoplasm Circulating Cells: DE, drug effects
Neoplasm Circulating Cells: PA, pathology

Ricin: AE, adverse effects
Ricin: IM, immunology
Ricin: TU, therapeutic use
Treatment Outcome

L28 ANSWER 4 OF 18 MEDLINE
AN 1998135704 MEDLINE
DN 98135704 PubMed ID: 9476837
TI The effectiveness of mailed patient reminders on mammography screening: a meta-analysis.
AU Wagner T H
CS School of Public Health, University of California, Berkeley 94720-7360, USA.
NC GK09 405940 31028
SO AMERICAN JOURNAL OF PREVENTIVE MEDICINE, (1998 Jan) 14 (1) 64-70. Journal code: APL; 8704773. ISSN: 0749-3797.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE) (META-ANALYSIS)
LA English
FS Priority Journals
EM 199804
ED Entered STN: 19980416
Last Updated on STN: 19980416
Entered Medline: 19980403
AB BACKGROUND: Researchers have tried to increase mammography screening rates by using patient-oriented reminders. This paper compares the effectiveness of mailed patient reminders at increasing mammography screening. METHODS: Sixteen published articles met the inclusion criteria and were included in the meta-analysis. To assess the association between reminders and mammography screening, the Mantel-Haenszel odds ratio (OR) was calculated. RESULTS: Among U.S. studies in which controls did not receive any type of reminder, women who received reminders were approximately 50% more likely to get a mammogram (OR 1.48; chi(2)**MH**(**1**) = 38.27, P < .001). In addition, tailored letters were found to be more effective than generic reminders (OR 1.87; chi(2)**MH**(**1**) = 4.70, P < .05). Combining cost and effectiveness data allowed for estimates of cost per woman screened, which ranged from $0.96 to $5.88. CONCLUSIONS: Patient reminders are effective at increasing mammography screening. More research is needed to assess (1) the cost-effectiveness of patient reminders and (2) their effectiveness across race, education, income, and type of insurance.
CT Check Tags: Female; Human; Support, U.S. Gov't, P.H.S.
***Breast Neoplasms: PC, prevention & control**
Costs and Cost Analysis
Follow-Up Studies
Mammography: EC, economics
*Mammography: SN, statistics & numerical data
*Mass Screening: OG, organization & administration
Mass Screening: SN, statistics & numerical data
Odds Ratio
Patient Compliance
*Program Development: MT, methods
Randomized Controlled Trials
Reminder Systems: EC, economics
*Reminder Systems: SN, statistics & numerical data
Sensitivity and Specificity
United States

L28 ANSWER 5 OF 18 MEDLINE
AN 1998060590 MEDLINE
DN 98060590 PubMed ID: 9399669
TI Soluble HER-2/neu neutralizes biologic effects of anti-HER-2/neu antibody

on breast cancer cells in vitro.
AU Brodowicz T; Wiltschke C; Budinsky A C; Krainer M; Steger G G; Zielinski C C
CS Clinical Division of Oncology, University Hospital, Vienna, Austria.
SO INTERNATIONAL JOURNAL OF CANCER, (1997 Dec 10) 73 (6) 875-9.
Journal code: GQU; 0042124. ISSN: 0020-7136.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199801
ED Entered STN: 19980122
Last Updated on STN: 20000303
Entered Medline: 19980108
AB Amplification and over-expression of the HER-2/neu proto-oncogene are associated with poor prognosis in women with both node-positive and node-negative breast cancer. Therefore, the encoded surface glycoprotein represents an attractive target for cancer immunotherapies. Furthermore, the extracellular domain of HER-2/neu is released from the cell surface by **proteolytic** cleavage. In the present experiments, we investigated the potential biologic effects of soluble HER-2/neu with particular emphasis on its interaction with anti-HER-2/neu antibodies. A monoclonal antibody specific for the extracellular domain of HER-2/neu dose dependently inhibited the proliferation of highly HER-2/neu-expressing SK-BR-3 and BT-474 breast cancer cells but had no effect on the proliferation of weakly to moderately HER-2/neu-expressing MCF-7, HBL-100 and ZR-75-1 breast cells. Addition of SK-BR-3 or BT-474 cell supernatants with high concentrations of soluble HER-2/neu led to a neutralization of anti-HER-2/neu antibody-mediated inhibition of proliferation due to a binding of soluble HER-2/neu by the antibody, which could be demonstrated by immunoprecipitation. Furthermore, the ability of anti-HER-2/neu antibodies to mediate antibody-dependent cellular cytotoxicity (ADCC) by lymphokine-activated killer cells was assessed. Cytolysis of SK-BR-3 tumor cells was increased significantly in the presence of anti-HER-2/neu antibodies. Similar to the proliferation inhibition, ADCC was neutralized by addition of soluble HER-2/neu-containing supernatants. Our data suggest that tumors rich in HER-2/neu might thus escape certain steps of immunologic control by neutralizing biologic activities of anti HER-2/neu antibodies due to the presence of soluble HER-2/neu.
CT Check Tags: Female; Human
Antibodies, Monoclonal: IM, immunology
***Antibodies, Monoclonal: TU, therapeutic use**
Antibody-Dependent Cell Cytotoxicity
Breast: CY, cytology
Breast: IM, immunology
Breast Neoplasms: IM, immunology
Breast Neoplasms: PA, pathology
***Breast Neoplasms: TH, therapy**
Cell Division
Cells, Cultured
Culture Media, Conditioned
Immunotherapy
Receptor, erbB-2: AN, analysis
*Receptor, erbB-2: IM, immunology
*Receptor, erbB-2: PH, physiology
Solubility
Tumor Cells, Cultured

L28 ANSWER 6 OF 18 MEDLINE
AN 1998022445 MEDLINE
DN 98022445 PubMed ID: 9359487
TI Cure of malignant ascites and generation of protective immunity by monoclonal antibody-targeted activation of a glucuronide prodrug in rats.

AU Chen B M; Chan L Y; Wang S M; Wu M F; Chern J W; Roffler S R
CS Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan.
SO INTERNATIONAL JOURNAL OF CANCER, (1997 Nov 4) 73 (3) 392-402.
Journal code: GQU; 0042124. ISSN: 0020-7136.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199711
ED Entered STN: 19971224
Last Updated on STN: 19971224
Entered Medline: 19971117
AB We examined the in vivo efficacy of targeting beta-glucuronidase (betaG) to activate a glucuronide prodrug (BHAMG) of p-hydroxyaniline mustard (pHAM) at hepatoma ascites in Sprague-Dawley rats. Injection i.p. of 500 microg RH1-betaG, a conjugate formed between recombinant betaG and monoclonal antibody RH1 with specificity for an antigen expressed on AS-30D rat hepatoma cells, into rats bearing AS-30D ascites resulted in the accumulation of 54 microg conjugate per 10(9) tumor cells after 2 hr. Ascites fluid and serum contained 0.53 and 0 microg/ml, respectively, RH1-betaG 2 hr after injection of the conjugate. Conjugate binding to AS-30D cells was heterogeneous and non-saturated, as determined by flow cytometry. BHAMG was less toxic than pHAM to SD rats based on measures of animal mortality, weight loss and hematological toxicity. Treatment of rats bearing established hepatoma ascites with 500 microg RH1-betaG followed 2 hr later with a single i.p. injection of 30 mg/kg BHAMG or 3 i.p. injections of 10 mg/kg BHAMG 2, 3 and 4 hr later resulted in the cure of 6/8 and 8/8 animals, respectively. Treatment with BHAMG or pHAM alone did not produce cures, whereas treatment with a control antibody-betaG conjugate and BHAMG produced significantly greater hematological toxicity compared to treatment with RH1-betaG and BHAMG. All cured rats were completely protected from rechallenge with 2 x 10(7) AS-30D cells, indicating that successful treatment of animals induced protective immunity.
CT Check Tags: Animal; Support, Non-U.S. Gov't
*Aniline Mustard: AA, analogs & derivatives
Aniline Mustard: ME, metabolism
Aniline Mustard: TU, therapeutic use
Aniline Mustard: TO, toxicity
Antibodies, Monoclonal: TU, therapeutic use
Antineoplastic Agents: ME, metabolism
*Antineoplastic Agents: TU, therapeutic use
Antineoplastic Agents: TO, toxicity
Ascites: ME, metabolism
*Ascites: TH, therapy
Carcinoma, Hepatocellular: ME, metabolism
***Carcinoma, Hepatocellular: TH, therapy**
***Glucuronidase: ME, metabolism**
Immunotoxins: ME, metabolism
***Immunotoxins: TU, therapeutic use**
Leukocytes: DE, drug effects
Liver Neoplasms: ME, metabolism
***Liver Neoplasms: TH, therapy**
Lymphocytes: DE, drug effects
Mice
Mice, Inbred BALB C
Mice, SCID
Prodrugs: ME, metabolism
*Prodrugs: TU, therapeutic use
Prodrugs: TO, toxicity
Rats
Rats, Sprague-Dawley
Tumor Cells, Cultured: DE, drug effects

L28 ANSWER 7 OF 18 MEDLINE
AN 97341968 MEDLINE
DN 97341968 PubMed ID: 9198168
TI Clinical impact of the plasminogen activation system in tumor invasion and metastasis: prognostic relevance and target for therapy.
AU Schmitt M; Harbeck N; Thomssen C; Wilhelm O; Magdolen V; Reuning U; Ulm K; Hofler H; Janicke F; Graeff H
CS Frauenklinik und Poliklinik, Technischen Universitat Munchen, Germany.. manfred.schmitt@lrz.tu-muenchen.de
SO THROMBOSIS AND HAEMOSTASIS, (1997 Jul) 78 (1) 285-96. Ref: 128
Journal code: VQ7; 7608063. ISSN: 0340-6245.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
FS Priority Journals
EM 199708
ED Entered STN: 19970825
Last Updated on STN: 19970825
Entered Medline: 19970808
AB Extravasation and intravasation of solid malignant tumors is controlled by attachment of tumor cells to components of the basement membrane and the extracellular matrix, by local proteolysis and tumor cell migration. Strong clinical and experimental evidence has accumulated that the tumor-associated serine protease plasmin, its activator uPA (urokinase-type plasminogen activator), the receptor uPA-R (CD87), and the inhibitors PAI-1 and PAI-2 are linked to cancer invasion and metastasis. In cancer, increase of uPA, uPA-R, and/or PAI-1 is associated with tumor progression and with shortened disease-free and/or overall survival in patients afflicted with malignant solid tumors. uPA and/or its inhibitor PAI-1 appear to be one of the strongest prognostic markers so far described. Strong prognostic value to predict disease recurrence and overall survival has been documented for patients with cancer of the breast, ovary, cervix, endometrium, stomach, colon, lung, bladder, kidney, brain, and soft-tissue. Due to the strong correlation between elevated uPA and/or PAI-1 values in primary cancer tissues and the tumor invasion/ metastasis capacity of cancer cells, **proteolytic** factors have been selected as targets for therapy. Various very different approaches to interfere with the expression or reactivity of uPA or CD87 at the gene or protein level were successfully tested including antisense oligonucleotides, antibodies, enzyme inhibitors, and recombinant or synthetic uPA and uPA-R analogues.
CT Check Tags: Human; Support, Non-U.S. Gov't
Antibodies, Monoclonal: TU, therapeutic use
Neoplasm Invasiveness
Neoplasm Metastasis
Neoplasms: PA, pathology
Neoplasms: PP, physiopathology
***Neoplasms: TH, therapy**
Oligonucleotides, Antisense: TU, therapeutic use
*Plasminogen Activators
Prognosis
Survival Rate

L28 ANSWER 8 OF 18 MEDLINE
AN 96320473 MEDLINE
DN 96320473 PubMed ID: 8764123
TI ZD2767, an improved system for antibody-directed enzyme prodrug therapy that results in tumor regressions in colorectal tumor xenografts.
AU Blakey D C; Burke P J; Davies D H; Dowell R I; East S J; Eckersley K P; Fitton J E; McDaid J; Melton R G; Niculescu-Duvaz I A; Pinder P E; Sharma

S K; Wright A F; Springer C J
CS Cancer, Metabolism, and Endocrine Research Department, Zeneca Pharmaceuticals, Alderley Park, Macclesfield, Cheshire, United Kingdom.
SO CANCER RESEARCH, (1996 Jul 15) 56 (14) 3287-92.
Journal code: CNF; 2984705R. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199609
ED Entered STN: 19961008
Last Updated on STN: 20000303
Entered Medline: 19960920
AB ZD2767 represents an improved version of antibody-directed enzyme prodrug therapy. It consists of a conjugate of the F(ab')2 A5B7 antibody fragment and carboxypeptidase G2 (CPG2) and a prodrug, 4-[N,N-bis(2-iodoethyl)amino]phenoxycarbonyl L-glutamic acid. The IC50 of the prodrug against LoVo colorectal tumor cells was 47 microM, and cleavage by CPG2 released the potent bis-iodo phenol mustard drug (IC50 = 0.34 microM). The drug killed both proliferating and quiescent LoVo cells. Administration of the ZD2767 conjugate to nude mice bearing LoVo colorectal xenografts resulted in approximately 1% of injected ZD2767 conjugate localizing/g of tumor after 72 h, and blood and normal tissue levels of the conjugate were 10-50-fold lower. A single round of therapy involving the administration of the prodrug 72 h after the conjugate to athymic mice bearing established LoVo xenografts resulted in approximately 50% of the tumors undergoing complete regressions, tumor growth delays greater than 30 days, and little toxicity (as judged by body-weight loss). Similar studies using a control antibody-CPG2 conjugate that does not bind to LoVo tumor cells resulted in a growth delay of less than 5 days, confirming the tumor specificity of this approach. These studies demonstrate the potential of ZD2767 for the treatment of colorectal cancer.
CT Check Tags: Animal; Female; Human; Support, Non-U.S. Gov't
Antibodies, Monoclonal: TU, therapeutic use
Antibodies, Neoplasm: TU, therapeutic use
*Antineoplastic Agents, Alkylating: AD, administration & dosage
***Colorectal Neoplasms: DT, drug therapy**
Immunotoxins: AD, administration & dosage
Mice
Mice, Nude
Neoplasm Transplantation
*Nitrogen Mustard Compounds: AD, administration & dosage
*Prodrugs: AD, administration & dosage
Transplantation, Heterologous
gamma-Glutamyl Hydrolase: ME, metabolism

L28 ANSWER 9 OF 18 MEDLINE
AN 96288860 MEDLINE
DN 96288860 PubMed ID: 8727948
TI Serial growth of human malignant fibrous histiocytoma xenografts in immunodeficient mice.
AU Kurihara N; Kubota T; Otani Y; Watanabe M; Kumai K; Kitajima M
CS Department of Surgery, School of Medicine, Keio University, Tokyo, Japan.
SO SURGERY TODAY, (1996) 26 (4) 267-70.
Journal code: BFY; 9204360. ISSN: 0941-1291.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199610
ED Entered STN: 19961015
Last Updated on STN: 19970203
Entered Medline: 19961002

AB Malignant fibrous histiocytoma (MFH) is on of the most common soft tissue sarcomas of adulthood, the only treatment for which involves surgical resection of the extremities and retroperitoneum, while no standard postoperative adjuvant chemotherapy has been established. We report herein on the establishment of a serially transplantable MFH strain in immunodeficient mice. An intraperitoneal tumor was resected from a patient with multiple recurrent MFH, inoculated into the subcutaneous tissue of mice with severe combined immunodeficiency (SCID), and established as a serially transplantable MFH strain, **MH-1**. The chemosensitivity of **MH-1** was similar to that of the original fresh surgical specimen, as confirmed by the 3-(4,5-dimethyl-2-thiazolyl)-2, 5-diphenyl-2H tetrazolium bromide (MTT) test. We believe that this serially transplantable strain will be useful for further studies on chemotherapy effective against MFH.

CT Check Tags: Animal; Case Report; Human
Abdominal Neoplasms: PA, pathology
Abdominal Neoplasms: SU, surgery
*Cell Division: PH, physiology
*Histiocytoma, Fibrous: PA, pathology
Histiocytoma, Fibrous: SU, surgery
Ileal Neoplasms: PA, pathology
Ileal Neoplasms: SU, surgery
Mice
Mice, SCID
Middle Age
Neoplasm Recurrence, Local: PA, pathology
Neoplasm Recurrence, Local: SU, surgery
Neoplasm Transplantation
Reoperation
*Soft Tissue Neoplasms: PA, pathology
Soft Tissue Neoplasms: SU, surgery
Tumor Cells, Cultured
Tumor Stem Cell Assay

L28 ANSWER 10 OF 18 MEDLINE
AN 96160043 MEDLINE
DN 96160043 PubMed ID: 8562906
TI Targeted therapy of carcinomas using BR96 sFv-PE40, a single-chain immunotoxin that binds to the Le(y) antigen.
AU Siegall C B
CS Molecular Immunology Department, Bristol-Myers Squibb, Pharmaceutical Research Institute, Seattle, WA 98121, USA.
SO SEMINARS IN CANCER BIOLOGY, (1995 Oct) 6 (5) 289-95. Ref: 44
Journal code: A6Y; 9010218. ISSN: 1044-579X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199603
ED Entered STN: 19960315
Last Updated on STN: 19960315
Entered Medline: 19960307
AB Monoclonal antibody BR96 recognizes a Le(y)-related carbohydrate antigen expressed on a wide range of carcinomas. Immunotoxins composed of BR96 and a binding defective form of Pseudomonas exotoxin A were constructed both as chemical conjugates and as fusion proteins. While both forms of BR96 immunotoxin were equally cytotoxic to human carcinoma cell lines in vitro, the fusion protein form, BR96 sFv-PE40, was > 10-fold more active in vivo as an antitumor agent. BR96 sFv-PE40 was used to target established human tumor xenografts in both mice and in rats. The rat which displays the Le(y) antigen on the same normal tissues as humans appears to be an

appropriate model for the preclinical evaluation of this immunotoxin. Complete regressions of lung, breast and bladder carcinomas were obtained in these models upon administration of well-tolerated doses of BR96 sFv-PE40. The clinical limitations of BR96 sFv-PE40, as well as other immunotoxins, depend on the management and/or prevention of neutralizing anti-immunotoxin antibodies and the onset of toxicities, specifically vascular leak syndrome.

CT Check Tags: Animal; Human
Antibodies, Monoclonal: TU, therapeutic use
Capillary Permeability
*Exotoxins: TU, therapeutic use
IgG: TU, therapeutic use
Immunoglobulin Fragments: TU, therapeutic use
***Immunotoxins: TU, therapeutic use**
*Lewis Blood-Group System: IM, immunology
Mice
***Neoplasms, Experimental: TH, therapy**
Rats

L28 ANSWER 11 OF 18 MEDLINE
AN 95300130 MEDLINE
DN 95300130 PubMed ID: 7780984
TI Identification of a monoclonal antibody, TV-1, directed against the basement **membrane** of **tumor** vessels, and its use to enhance the delivery of macromolecules to tumors after conjugation with interleukin 2.
AU Epstein A L; Khawli L A; Hornick J L; Taylor C R
CS Department of Pathology, University of Southern California School of Medicine, Los Angeles 90033, USA.
NC 1 RO1 CA49987 (NCI)
2 RO1 CA47334 (NCI)
SO CANCER RESEARCH, (1995 Jun 15) 55 (12) 2673-80.
Journal code: CNF; 2984705R. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199507
ED Entered STN: 19950726
Last Updated on STN: 19980206
Entered Medline: 19950719
AB mAbs reactive with epitopes expressed on tumor vessels were evaluated as universal delivery agents of peptides with vasoactive properties to enhance the uptake of macromolecules in tumors. Unlike other reported approaches to target tumor vessels, a mAb designated TV-1 targets a basement membrane antigen that is found in all tissues but that is accessible only in tumor vessels, making it an alternative vehicle for the delivery of biologically active peptides to tumors. A panel of 30 monoclonal and polyclonal antibodies was screened by immunohistochemistry on sections of human tumors, normal vascular endothelium, and connective tissues. Five antibodies were chosen for in vivo evaluation, including two antifibronectin antibodies (TV-1, HFN 7.1), one anti-basic fibroblast growth factor antibody (anti-BFGF), and two antibodies reactive with a mesenchymal cell antigen (TP-1, TP-3). Three nude mouse tumor models characterized by varying degrees of vascularization (low to high) were used. After chemical conjugation to interleukin 2 (IL-2), these antibodies were used to pretreat tumor-bearing nude mice 3 h before injection with a radiolabeled mAb directed to the transplanted tumors. Pretreatment with TV-1/IL-2 or HFN 7.1/IL-2 produced a 3-fold higher tumor uptake of radiolabel compared to control mice pretreated with mAb alone. The other three vasoactive immunoconjugates failed to show significant increases in these tumor models. When TV-1/IL-2 was compared with the specific vasoconjugate (Lym-1/IL-2) as a pretreatment in the Raji lymphoma model,

which has low vascularization, TV-1/IL-2 yielded approximately 60% of the tumor uptake seen with Lym-1/IL-2. In comparison, pretreatment with TV-1/IL-2 in the LS174T colon carcinoma model, which has high vascularization, yielded approximately the same tumor uptake seen with the B72.3/IL-2 vasoconjugate, which directly targets the tumor cells. These studies demonstrate that a mAb directed against fibronectin in the endothelial subcellular matrix can be used to deliver vasoactive agents to tumors.

CT Check Tags: Animal; Human; Support, U.S. Gov't, P.H.S.
***Antibodies, Monoclonal: AD, administration & dosage**
Antibodies, Monoclonal: TU, therapeutic use
*Antigens, Neoplasm: AN, analysis
Antigens, Neoplasm: IM, immunology
*Basement Membrane: IM, immunology
Burkitt Lymphoma: IM, immunology
Burkitt Lymphoma: PA, pathology
Burkitt Lymphoma: PP, physiopathology
***Burkitt Lymphoma: TH, therapy**
Capillaries: PA, pathology
Cell Line
Drug Carriers
Immunohistochemistry
***Immunotoxins: AD, administration & dosage**
Immunotoxins: TU, therapeutic use
*Interleukin-2: AD, administration & dosage
Interleukin-2: TU, therapeutic use
Membrane Proteins: AN, analysis
Mice
Mice, Nude
Neoplasm Invasiveness
*Neoplasms: BS, blood supply
Neoplasms: PA, pathology
***Neoplasms: TH, therapy**
Tumor Cells, Cultured

L28 ANSWER 12 OF 18 MEDLINE
AN 92274362 MEDLINE
DN 92274362 PubMed ID: 1375534
TI Efficacy of an anti-CD7-ricin A chain immunoconjugate in a novel murine model of human T-cell leukemia.
AU Fishwild D M; Aberle S; Bernhard S L; Kung A H
CS Department of Immunology, XOMA Corporation, Berkeley, California 94710.
SO CANCER RESEARCH, (1992 Jun 1) 52 (11) 3056-62.
Journal code: CNF; 2984705R. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199206
ED Entered STN: 19920710
Last Updated on STN: 19960129
Entered Medline: 19920630
AB In vivo efficacy testing of monoclonal antibody-based drugs specific for human leukemias is hampered by the paucity of suitable animal models, due in part to the inability of many anti-human monoclonal antibodies to cross-react with antigens expressed in animal tissues or cells. Moreover, human leukemic cells have proven difficult to establish in immunosuppressed mice except as solid tumors. We report here the establishment of a murine model for human leukemia displaying features of human disease, such as growth of malignant cells and localization of such cells to lymphoid compartments, and the effective depletion of leukemic cells from these mice by an immunoconjugate. Human T-leukemia cells (CEM) injected into cyclophosphamide-pretreated NIH-III mice engrafted in all

mice (n = 41), with CEM cells detected in the bone marrow, spleen, and blood 4 weeks after injection. There was no evidence of solid tumors. Treatment of CEM-engrafted mice with 4A2-RTA30, an immunoconjugate of an anti-CD7 monoclonal antibody and ricin A chain (RTA30), resulted in a 100- to 200-fold overall depletion of CEM cells from the spleen and the bone marrow (P less than 0.02). This depletion was specific and toxin-dependent, as a control immunoconjugate had no demonstrable effect (P greater than 0.5). Depletion of CEM cells was also observed after treatment with unconjugated anti-CD7 mAb, but this effect was not significantly different from controls (P greater than 0.1). Therefore, significant depletion of CEM cells required the presence of the ricin A chain moiety. Further investigations revealed that CEM cells recovered from NIH-III mice expressed less CD7 antigen, but remained sensitive to subsequent in vitro exposure to 4A2-RTA30. In conclusion, we have established a model for studying the efficacy of immunoconjugates and have successfully depleted human T-leukemic cells from lymphoid tissues in immunodeficient mice by treatment with an anti-CD7-RTA30 immunoconjugate.

CT Check Tags: Animal; Comparative Study; Human; Male
Antibodies, Monoclonal: TU, therapeutic use
Antigens, CD: AN, analysis
*Antigens, CD: IM, immunology
Antigens, CD45
Antigens, CD7
*Antigens, Differentiation, T-Lymphocyte: IM, immunology
Cell Line
Cyclophosphamide: PD, pharmacology
Drug Administration Schedule
Drug Evaluation, Preclinical
Drug Screening Assays, Antitumor
Histocompatibility Antigens: AN, analysis
Immunosuppression
***Immunotoxins: TU, therapeutic use**
Immunotoxins: TO, toxicity
***Leukemia, T-Cell, Acute: TH, therapy**
Membrane Glycoproteins: AN, analysis
Mice
Mice, Inbred Strains
Neoplasm Transplantation: MT, methods
*Ricin: TU, therapeutic use
Ricin: TO, toxicity
Transplantation, Heterologous

L28 ANSWER 13 OF 18 MEDLINE
AN 92257856 MEDLINE
DN 92257856 PubMed ID: 1813213
TI Antibody directed enzyme prodrug therapy (ADEPT): clinical report.
AU Bagshawe K D; Sharma S K; Springer C J; Antoniw P; Boden J A; Rogers G T; Burke P J; Melton R G; Sherwood R F
CS Department of Medical Oncology, Charing Cross and Westminster Medical School, London.
SO DISEASE MARKERS, (1991 May-Aug) 9 (3-4) 233-8.
Journal code: DIM; 8604127. ISSN: 0278-0240.
CY ENGLAND: United Kingdom
DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199206
ED Entered STN: 19920626
Last Updated on STN: 20000303
Entered Medline: 19920612
AB Following an extensive series of studies in nude mice with human xenografts a pilot scale clinical trial of antibody directed enzyme

prodrug therapy has been initiated. The principle is to activate a relatively inert prodrug to an active **cytotoxin** by a tumour located enzyme. In the first stage of the study a prodrug para-N-(mono-2-chloroethyl monomesyl)-aminobenzoyl glutamic acid was administered to six patients with advanced colorectal cancer in a dose escalating protocol. Nausea and vomiting occurred as the only discernible toxic effect at the higher dose levels. Three of these patients and two other patients with advanced disease have proceeded to the second stage of the study in which an antibody-enzyme conjugate was given IV, followed after 36-48 h by a galactosylated anti-enzyme antibody. When plasma enzyme levels had become undetectable the patients received multiple doses of the prodrug. At the lower doses toxicity was minimal as were clinical responses. Two patients received higher doses which resulted in myelosuppression and temporary regression of advanced disease. No complications resulted from administration of the antibody-enzyme complex or enzyme inactivating antibody. The myelosuppression is attributable to the relatively long half-life of the active drug formed from the prodrug used in the present study.

CT Check Tags: Human; Support, Non-U.S. Gov't
***Antibodies, Monoclonal: TU, therapeutic use**
*Antineoplastic Agents: AD, administration & dosage
***Colorectal Neoplasms: DT, drug therapy**
*Glutamates: AD, administration & dosage
Gonadotropins, Chorionic: IM, immunology
*Nitrogen Mustard Compounds: AD, administration & dosage
*Prodrugs: AD, administration & dosage
***gamma-Glutamyl Hydrolase: AD, administration & dosage**

L28 ANSWER 14 OF 18 MEDLINE
AN 92239871 MEDLINE
DN 92239871 PubMed ID: 1373967
TI In vivo efficacy of B43 (anti-CD19)-pokeweed antiviral protein immunotoxin against human pre-B cell acute lymphoblastic leukemia in mice with severe combined immunodeficiency.
AU Uckun F M; Manivel C; Arthur D; Chelstrom L M; Finnegan D; Tuel-Ahlgren L; Irvin J D; Myers D E; Gunther R
CS Department of Therapeutic Radiology-Radiation Oncology, University of Minnesota Health Sciences Center, Minneapolis.
NC R01 CA-42633 (NCI)
R01 CA-44114 (NCI)
R01 CA-51425 (NCI)
+
SO BLOOD, (1992 May 1) 79 (9) 2201-14.
Journal code: A8G; 7603509. ISSN: 0006-4971.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199205
ED Entered STN: 19920619
Last Updated on STN: 19990129
Entered Medline: 19920529
AB A highly aggressive subclone of the human CALLA+C mu+ pre-B acute lymphoblastic leukemia (ALL) cell line NALM-6 (designated NALM-6-UM1) caused disseminated and fatal leukemia in CB.17 mice with severe combined immunodeficiency (SCID). An intravenous challenge with 1 x 10(6) (NALM-6-UM1 cells caused 15 of 27 (56%) SCID mice to become paraplegic at 31 +/- 2 days (median = 33 days) and 27 of 27 (100%) mice to die of disseminated leukemia at 38 +/- 1 days (median = 39 days). We used this SCID mouse model of aggressive human pre-B ALL to evaluate the in vivo antileukemic efficacy of B43 (anti-CD19)-pokeweed antiviral protein (PAP) immunotoxin. A 3-day treatment with nontoxic doses of B43-PAP markedly reduced the incidence of paraplegia and improved event-free survival (EFS)

in SCID mice challenged with 1 x 10(6) NALM-6-UM1 pre-B ALL cells, as reflected by significantly higher cumulative proportions of mice free of paraplegia or alive at 1 to 7 months, as compared with phosphate-buffered saline (PBS) treated control mice. The Kaplan-Meier estimates and standard errors of the probability of developing paraplegia after inoculation of 1 x 10(6) NALM-6-UM1 cells was 64% +/- 10% for PBS-treated mice (median time to paraplegia = 37 days) (N = 27), 18% +/- 8% for mice treated with 15 micrograms B43-PAP (5 micrograms/mouse/d x 3 days) (N = 23) and 5% +/- 5% for mice treated with 30 micrograms B43-PAP (10 micrograms/mouse/d x 3 days) (N = 21). While 27 of 27 PBS-treated control SCID mice died of leukemia at 38 +/- 1 days (range = 24 to 54 days), only 16 of 44 B43-PAP-treated mice developed leukemia at 74 +/- 12 days (range = 30 to 182 days), consistent with greater than or equal to 6 logs kill of clonogenic NALM-6-UM1 cells in 64% of SCID mice. The Kaplan-Meier estimates and standard errors of the probability of long-term EFS after inoculation of 1 x 10(6) NALM-6-UM1 cells were 65% +/- 10% for mice treated with 15 micrograms B43-PAP and 60% +/- 11% for mice treated with 30 micrograms B43-PAP with a median survival time of greater than 7 months for both groups. In contrast, neither unconjugated B43 monoclonal antibody nor the anti-T-cell immunotoxin G17.2 (anti-CD4)-PAP decreased the incidence of paraplegia or improved EFS.(ABSTRACT TRUNCATED AT 400 WORDS)

CT Check Tags: Animal; Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.

***Antibodies, Monoclonal: TU, therapeutic use**
Antigens, CD: AN, analysis
*Antigens, CD: IM, immunology
Antigens, CD19
Antigens, CD45
Antigens, Differentiation: AN, analysis
*Antigens, Differentiation, B-Lymphocyte: IM, immunology
Antigens, Neoplasm: AN, analysis
*Antineoplastic Agents, Phytogenic: TU, therapeutic use
Chromosome Aberrations
Histocompatibility Antigens: AN, analysis
***Immunotoxins: TU, therapeutic use**
Leukemia, B-Cell, Acute: GE, genetics
***Leukemia, B-Cell, Acute: TH, therapy**
Mice
Mice, SCID
Neprilysin
*Plant Proteins: TU, therapeutic use

L28 ANSWER 15 OF 18 MEDLINE
AN 91274142 MEDLINE
DN 91274142 PubMed ID: 1711364
TI Structure of solid tumors and their vasculature: implications for therapy with monoclonal antibodies.
AU Dvorak H F; Nagy J A; Dvorak A M
CS Department of Pathology, Beth Israel Hospital, Boston, Massachusetts.
SO CANCER CELLS, (1991 Mar) 3 (3) 77-85. Ref: 50
Journal code: AU5; 9000382. ISSN: 1042-2196.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199108
ED Entered STN: 19910818
Last Updated on STN: 19960129
Entered Medline: 19910801
AB Delivery of monoclonal antibodies to solid tumors is a vexing problem that must be solved if these antibodies are to realize their promise in

therapy. Such success as has been achieved with monoclonal antibodies is attributable to the local hyperpermeability of the tumor vasculature, a property that favors antibody extravasation at tumor sites and that is mediated by a **tumor**-secreted vascular **permeability** factor. However, leaky **tumor** blood vessels are generally some distance removed from target tumor cells, separated by stroma and by other tumor cells that together represent significant barriers to penetration by extravasated monoclonal antibodies. For this reason, alternative approaches may be attractive. These include the use of antibody-linked **cytotoxins**, which are able to kill tumor cells without immediate contact, and direction of antibodies against nontumor cell targets, for example, antigens unique to the tumor vascular endothelium or to tumor stroma.

CT Check Tags: Human
Antibodies, Monoclonal: PK, pharmacokinetics
***Antibodies, Monoclonal: TU, therapeutic use**
Antibodies, Neoplasm: PK, pharmacokinetics
Antibodies, Neoplasm: TU, therapeutic use
Capillary Permeability
Endothelium, Vascular: DE, drug effects
Extracellular Space: IM, immunology
Extracellular Space: ME, metabolism
Immunotoxins: PK, pharmacokinetics
Immunotoxins: TU, therapeutic use
Intercellular Junctions: UL, ultrastructure
Neoplasms: BS, blood supply
Neoplasms: PA, pathology
***Neoplasms: TH, therapy**
Neovascularization, Pathologic
Radioisotopes: AD, administration & dosage
Radioisotopes: TU, therapeutic use

L28 ANSWER 16 OF 18 MEDLINE
AN 90013364 MEDLINE
DN 90013364 PubMed ID: 2529399
TI In vitro and in vivo cytotoxic activity of anti-human leukemia monoclonal antibodies SN5c and SN6 daunorubicin conjugates.
AU Biddle W C; Haruta Y; Seon B K; Henderson E S; Sarcione E J
CS Department of Clinical Immunology, Roswell Park Memorial Institute, Buffalo, NY 14263.
NC P01 CA 42683 (NCI)
R01 CA19304 (NCI)
SO LEUKEMIA RESEARCH, (1989) 13 (8) 699-707.
Journal code: K9M; 7706787. ISSN: 0145-2126.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198911
ED Entered STN: 19900328
Last Updated on STN: 19970203
Entered Medline: 19891101
AB Murine monoclonal antibodies SN5c specific for the common acute lymphoblastic leukemia antigen (CALLA) and SN6 specific for a novel GP160 tumor associated antigen expressed on non-T ALL and myelomonocytic leukemia cells were conjugated to daunorubicin via an intermediate dextran carrier. The resulting monoclonal antibody-daunorubicin conjugates retained the immunoreactivity of the unlabeled antibody to antigen positive leukemia target cells. In addition, these conjugates demonstrated selective cytotoxic activity when tested against a panel of human leukemia cell lines and/or human leukemia patient samples of peripheral blood or bone marrow origin. The SN5c and SN6-daunorubicin immunoconjugates were superior to a non-specific isotype matched MOPC-daunorubicin conjugate in

in vitro cytotoxicity assays. Free daunorubicin, however, was more cytotoxic than either immunoconjugate but lacked selectivity. SN5c-daunorubicin and SN6-daunorubicin combined were as effective as free daunorubicin when used for in vivo therapy and led to complete ablation of established NALM-6 tumors in an athymic nude mouse model. The SN5c-daunorubicin conjugate was also shown to be significantly less toxic than free daunorubicin in non-tumor bearing Balb/c mice. These studies indicate that mAb-daunorubicin conjugates can be constructed which retain specific binding and exhibit selective cytotoxicity against human leukemia cells and suggest that they may have therapeutic applications.

CT Check Tags: Animal; Female; Human; Support, U.S. Gov't, P.H.S.
Antibodies, Monoclonal: TU, therapeutic use
Antibodies, Monoclonal: TO, toxicity
*Antigens, Differentiation: IM, immunology
*Antigens, Neoplasm: IM, immunology
Cell Line
Cell Survival: DE, drug effects
Daunorubicin: PD, pharmacology
*Daunorubicin: TU, therapeutic use
Daunorubicin: TO, toxicity
Drug Screening Assays, Antitumor
***Fibrosarcoma: DT, drug therapy**
Immunotoxins: PD, pharmacology
***Immunotoxins: TU, therapeutic use**
Immunotoxins: TO, toxicity
Leukemia
Lymphocytes: CY, cytology
Lymphocytes: DE, drug effects
Mice
Mice, Inbred BALB C
Mice, Nude
Neoplasm Transplantation
Neprilysin

L28 ANSWER 17 OF 18 MEDLINE
AN 90003000 MEDLINE
DN 90003000 PubMed ID: 2790828
TI Phase I study of monoclonal antibody-ricin A chain immunotoxin XomaZyme-791 in patients with metastatic colon cancer.
AU Byers V S; Rodvien R; Grant K; Durrant L G; Hudson K H; Baldwin R W; Scannon P J
CS XOMA Corporation, Berkeley, California.
SO CANCER RESEARCH, (1989 Nov 1) 49 (21) 6153-60.
Journal code: CNF; 2984705R. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198911
ED Entered STN: 19900328
Last Updated on STN: 19900328
Entered Medline: 19891120

AB Monoclonal antibody 791T/36, recognizing a Mr 72,000 antigen on the surface of colon carcinoma cells, has been used to construct an immunotoxin by conjugating to it the ribosomal inhibitor protein, ricin toxin A chain. The antibody 791T/36 has been shown to bind to **membranes** of freshly disaggregated **tumor** cells from human colon tumors, and to localize in tumors in vivo. Subacute toxicology testing in rats receiving immunotoxin i.v. showed, at highest doses, weight loss, decreased serum albumin, and hepatocyte vacuolization without elevation in liver function tests. A Phase I dose escalation study was carried out in which 17 patients with metastatic colorectal cancer were treated with doses of immunotoxin ranging from 0.02 to 0.2 mg/kg/day in

1-h i.v. infusions for a 5-day course. Side-effects included a composite of signs and symptoms thought to be generic to ricin A chain immunotoxins, including decreased serum albumin, mild fever, and flu-like symptoms, all being reversible. Two additional findings, reversible proteinuria and mental status changes, were also noted which may be characteristic of this immunotoxin. By 10-20 days after therapy, most patients developed IgM and IgG antibodies against both the ricin toxin A chain and the immunoglobulin portion of the immunotoxin, which were asymptomatic. A strong anticombining site antibody response was seen. Biological activity manifest as mixed tumor regression was seen in five patients.

CT Check Tags: Animal; Female; Human; Male
Adult
Aged
***Antibodies, Monoclonal: AE, adverse effects**
Antibodies, Monoclonal: TU, therapeutic use
Antibodies, Monoclonal: TO, toxicity
Antibody Formation
Carcinoembryonic Antigen: AN, analysis
Colonic Neoplasms: IM, immunology
***Colonic Neoplasms: TH, therapy**
Drug Evaluation
Enzyme-Linked Immunosorbent Assay
IgG: AN, analysis
IgM: AN, analysis
***Immunotoxins: AE, adverse effects**
Immunotoxins: TU, therapeutic use
Immunotoxins: TO, toxicity
Lethal Dose 50
Liver Function Tests
Liver Neoplasms: IM, immunology
*Liver Neoplasms: SC, secondary
Liver Neoplasms: TH, therapy
Lung Neoplasms: IM, immunology
*Lung Neoplasms: SC, secondary
Lung Neoplasms: TH, therapy
Mice
Mice, Inbred BALB C
Middle Age
Neoplasm Metastasis
Rats
Rats, Inbred Strains
*Ricin: AE, adverse effects
Ricin: TU, therapeutic use
Ricin: TO, toxicity
Serum Albumin: AN, analysis

L28 ANSWER 18 OF 18 MEDLINE
AN 88282409 MEDLINE
DN 88282409 PubMed ID: 2969282
TI Efficient transplantation of human non-T-leukemia cells into nude mice and induction of complete regression of the transplanted distinct tumors by ricin A-chain conjugates of monoclonal antibodies SN5 and SN6.
AU Hara H; Luo Y; Haruta Y; Seon B K
CS Department of Molecular Immunology, Roswell Park Memorial Institute, Buffalo, New York 14263.
NC CA19304 (NCI)
CA42683 (NCI)
SO CANCER RESEARCH, (1988 Aug 15) 48 (16) 4673-80.
Journal code: CNF; 2984705R. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals

EM 198809
ED Entered STN: 19900308
Last Updated on STN: 19970203
Entered Medline: 19880908

AB In the present study, we established a dependable system by which human pre-B- and non-T/non-B-acute lymphoblastic leukemia (ALL) cells are efficiently transplanted into nude mice; the transplanted tumors provide a useful model for investigating the efficacy of antitumor agents in the in vivo therapy of human cancer. NALM-6 (a pre-B-ALL cell line) cells were transplanted under varying conditions as the pre-B-leukemia cells, whereas REH (a non-T/non-B-ALL cell line) cells were transplanted as the non-T/non-B-leukemia cells. Under optimal and near optimal conditions, 71 of 101 X-irradiated mice (70%) developed distinct tumors approximately 2 wk after i.d. inoculation of a mixture of NALM-6 cells and X-irradiated human fibrosarcoma cells. Under the same conditions, 9 of 11 mice (82%) developed tumors following i.d. inoculation of REH cells admixed with X-irradiated human fibrosarcoma cells. Examination of the tumor tissues demonstrated that the tumors are of leukemia origin but not of fibrosarcoma origin. To demonstrate the usefulness of the present tumors for investigating the efficacy of antitumor agents in the in vivo therapy of human cancer, immunotoxins were tested for their specific suppressive activity against growing tumors of the transplanted NALM-6 cells. To this end, monoclonal antibodies SN5 and SN6 which define a common ALL antigen, termed CALLA, and a novel leukemia-associated cell surface glycoprotein, termed gp160, respectively, were separately conjugated with the A-chain subunit of ricin, a plant toxin; CALLA and gp160 are expressed on the cell surface of various human non-T-leukemia cells including NALM-6 cells. The conjugates of SN5 and SN6 with ricin A-chain (RA) showed specific activity against the leukemia cells but not against control cells in an in vitro assay. To investigate their in vivo efficacy in suppressing tumor growth, nude mice which had been inoculated i.d. with NALM-6 cells 25 days in advance and bore distinct palpable tumors (5 to 6 mm in diameter) were divided into five groups. One group of mice was nontreated as a control. Each of the remaining four groups of mice was given an injection of one of the following agents: (a) purified control mouse IgG (IgG1); (b) purified antibodies SN5 (IgG1) and SN6 (IgG1); (c) control IgG-RA conjugate; or (d) SN5-RA and SN6-RA. Tumors in all mice of the first four groups including the untreated group grew continuously, causing the mice to die.(ABSTRACT TRUNCATED AT 400 WORDS)

CT Check Tags: Animal; Female; Support, U.S. Gov't, P.H.S.
Ammonium Chloride: PD, pharmacology
Antibodies, Monoclonal: TU, therapeutic use
*Antigens, Differentiation: IM, immunology
*Antigens, Neoplasm: IM, immunology
***Immunotoxins: AD, administration & dosage**
Immunotoxins: PD, pharmacology
***Immunotoxins: TU, therapeutic use**
Leukemia, Experimental: PA, pathology
***Leukemia, Experimental: TH, therapy**
Mice
Mice, Inbred BALB C
Neoplasm Metastasis
Neoplasm Transplantation
Neprilysin
*Ricin: AD, administration & dosage
Ricin: PD, pharmacology
Transplantation, Heterologous
Tumor Cells, Cultured

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=> fil wpids
FILE 'WPIDS' ENTERED AT 14:42:24 ON 22 OCT 2001
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FILE LAST UPDATED: 18 OCT 2001              <20011018/UP>
MOST RECENT DERWENT UPDATE           200160   <200160/DW>
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                DEL HIS Y
L1         31309 S TUMOR# OR TUMOUR# OR CARCINOMA# OR SARCOMA#
L2         10136 S MONOCLONAL
L3          2281 S L1 AND L2
L4          5210 S IMMUNOTOXIN# OR IMMUNO TOXIN# OR CYTOTOX?
L5           371 S L3 AND L4
L6         17044 S LIPASE# OR PROTEASE? OR PROTEINASE#  OR LIPOLYTIC OR PROTEOLY
L7            12 S L5 AND L6
L8         88129 S PERMEAB?
L9             4 S L5 AND L8
L10        12685 S VASCULA?
L11           22 S L5 AND L10
L12          316 S L10 (5A) (INCREAS?)
L13            0 S L11 AND L12
L14         5925 S CELL (3A) MEMBRANE#
L15           16 S L5 AND L14
L16          786 S L14 (L) (WEAK? OR PERMEAB? OR OPEN?)
L17            0 S L15 AND L16
L18          251 S L1 (5A) DAMAG?
L19            1 S L15 AND L18
L20       103106 S PENETRAT?
L21            1 S L20 AND L15
L22            6 S L5 AND L18
L23            1 S L20 AND L14 AND L5
L24           22 S L7 OR L9 OR L19 OR L21 OR L22 OR L23

     FILE 'WPIDS' ENTERED AT 14:42:24 ON 22 OCT 2001

=> d .wp 1-22

L24  ANSWER 1 OF 22  WPIDS COPYRIGHT 2001   DERWENT INFORMATION LTD
AN   2001-541567 [60]   WPIDS
CR   2000-412154 [35]; 2000-452188 [38]; 2000-572271 [52]; 2000-628263 [55];
     2001-016509 [02]; 2001-090793 [52]; 2001-183260 [18]; 2001-226690 [20];
     2001-381384 [39]
DNN  N2001-402496       DNC C2001-161670
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TI An isolated polypeptide designated PRO256 useful for treating a cardiovascular, endothelial, or angiogenic disorder.
DC B04 C03 D16 S03
IN GURNEY, A L; KIRCHHOFER, D K; WOOD, W I
PA (GETH) GENENTECH INC
CYC 93
PI WO 2001059100 A2 20010816 (200160)* EN 120p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
ADT WO 2001059100 A2 WO 2000-US34756 20001219
PRAI US 2000-253665 20001128; WO 2000-US3565 20000211; WO 2000-US6884 20000315
AB WO 200159100 A UPAB: 20011018
NOVELTY - An isolated polypeptide (I) having at least 80% sequence identity to the fully defined 527 amino acid sequence (S1) given in the specification is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) an isolated nucleic acid (II) having at least 80% identity to a nucleotide sequence that encodes (S1) and 80% identity to the fully defined 4926 base pair sequences given in the specification (N1);

(2) a vector (III) comprising (II);

(3) a host cell (IV) comprising (III);

(4) a method (M1) for producing (I);

(5) a chimeric molecule (V) comprising (I) fused to a heterologous amino acid;

(6) an antibody (VI) which binds (I);

(7) an article of manufacture (VII) comprising:

(a) a composition comprising:

(i) (I);

(ii) an agonist of (I); or

(iii) an antagonist of (I);

(b) a container to hold the composition; and

(c) a label affixed to the container, or package insert include in the container, giving instructions for use;

(8) a method (M2) for identifying an agonist of (I) comprising:

(a) contacting cells and a test compound to be screened where a cellular response normally associated with (I) is induced; and

(b) determining the induction of cellular response to determine whether the test compound is an effective agonist;

(9) a method (M3) for identifying a compound that inhibits the activity of (I) comprising contacting a test compound with (I) and determining whether the activity is inhibited;

(10) a method (M4) for identifying a compound that inhibits the expression of (I) in a cell comprising contacting the cell with a test compound and determining whether the expression of (I) is inhibited;

(11) a compound (VIII) that inhibits expression of (I) in a mammalian cell;

(12) a method (M5) for diagnosing a disease or susceptibility to a disease which is related to a mutation in (N1) comprising determining the presence or absence of the mutation;

(13) a method (M6) of diagnosing a cardiovascular, endothelial, or angiogenic disorder in a mammal comprising analyzing the level of expression of a gene encoding (I) in (a) a test sample of tissue cells, and (b) in a control sample of known normal tissue cells, where the higher or lower expression level in the test sample compared to the control sample is indicative of a disorder;

(14) a method (M7) of diagnosing a cardiovascular, endothelial, or angiogenic disorder in a mammal comprising detecting the presence or

absence of (I) in a test sample or control sample as above;

(15) a method (M8) of diagnosing a cardiovascular, endothelial, or angiogenic disorder in a mammal comprising:

(a) contacting (VI) with a test sample; and

(b) detecting the formation of a complex between (VI) and (I), where the formation of a complex is indicative of a disorder;

(16) a method (M9) of determining the presence of (I) in a sample comprising contacting with (VI) and determining binding;

(17) a cardiovascular, endothelial, or angiogenic disorder kit (IX) comprising (VI);

(18) a recombinant retroviral particle (X) comprising a retroviral vector consisting of a promoter, a nucleic acid encoding (I) or agonist or antagonist of (I), and a signal sequence for cellular secretion of (I), where (X) is in association with retroviral structural proteins; and

(19) an ex vivo producer cell (XI) comprising a nucleic acid construct that expresses retroviral structural proteins and also comprises (X), where (XI) packages (X) in association with the structural proteins to produced recombinant retroviral particles.

ACTIVITY - Cardiant; tranquilizer; vulnerary; cytostatic; hepatotropic; nephrotropic.

No supporting data given.

MECHANISM OF ACTION - Endothelial growth inhibitor/stimulator; angiogenesis inhibitor/stimulator; hepatocyte growth factor protease inhibitor/stimulator; gene therapy (all claimed).

A time course study of the inhibition of 125I-single-chain hepatocyte growth factor (scHGF) conversion into its two chain mature HGF form by (I) was conducted. In the presence of (I) (at time intervals 0, 0.5 hr, 1 hr, 2 hr, and 4 hr), the scHGF was not converted into its two chain form, whereas in the absence of (I), serum-mediated conversion of scHGF occurs within the 4 hr incubation period.

USE - (I) or an agonist/antagonist of (I) may be used to treat a cardiovascular, endothelial, or angiogenic disorder in a mammal, especially a human with cardiac hypertrophy, trauma, a type of tumor, or age-related macular degeneration. (I) may be administered together with a cardiovascular, endothelial, or angiogenic agent, a chemotherapeutic agent, a growth inhibitory agent, or a cytotoxic agent.

In addition, (II) may also be used to treat the disorders above, preferably through administration via ex vivo gene therapy.

Furthermore, (I) or an agonist of (I) may be used to inhibit endothelial cell growth, angiogenesis, or protease activity of a hepatocyte growth factor, whereas an antagonist of (I) may be used to stimulate endothelial cell growth, angiogenesis, or protease activity of a hepatocyte growth factor.

Stimulation or inhibition of the protease activity of a hepatocyte growth factor is preferably carried out where a mammal has a cardiovascular, endothelial, or angiogenic disorder selected from peripheral vascular disease, hepatic or renal injury or a restinosis disorder (all claimed).

Dwg.0/5

L24 ANSWER 2 OF 22 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 2001-514533 [56] WPIDS
CR 2001-536417 [50]
DNC C2001-153762
TI Delivering a medicament e.g. minoxidil sulfate to an abnormal brain region and/or to a malignant **tumor** comprises administration of a potassium channel agonist other than bradykinin.
DC B04 B05 B07 C03
IN BLACK, K L; NINGARAJ, N S
PA (CEDA-N) CEDARS SINAI MEDICAL CENT
CYC 93
PI WO 2001054771 A2 20010802 (200156)* EN 61p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ

NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM
DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC
LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE
SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW

ADT WO 2001054771 A2 WO 2001-US2743 20010126
PRAI US 2000-615854 20000714; US 2000-491500 20000126
AB WO 200154771 A UPAB: 20011018
NOVELTY - Delivering a medicament (I) to an abnormal brain region and/or to a malignant **tumor** comprising administration of a potassium channel agonist (II) other than bradykinin to increase **permeability** to (I) of a capillary or arteriole delivering blood to cells of the abnormal brain region and/or to the **tumor**, is new.

DETAILED DESCRIPTION - Delivering a medicament (I) to an abnormal brain region and/or to a malignant **tumor** comprises administering a potassium channel agonist (II) other than bradykinin or its analogue to increase **permeability** to (I) of a capillary or arteriole delivering blood to cells of the abnormal brain region and/or to the **tumor** where (I) and (II) are administered simultaneously to achieve selective delivery to cells of the abnormal brain region and/or to the **tumor**.

INDEPENDENT CLAIMS are also included for the following:

(a) a composition comprising (I) and (II) formulated in a solution for delivery by intravascular infusion or injection; and

(b) a kit for enhancing delivery of (I) to an abnormal brain region and/or to a malignant **tumor** comprising (II) and instructions for using (II).

ACTIVITY - Cerebroprotective; Cytostatic.

MECHANISM OF ACTION - Selective potassium channel activator. Wistar rats bearing implanted glioma cells were infused with either NS-1619 or minoxidil sulfate at 7.5 micro g kg-1 min-1 for 15 minutes, the unidirectional transport constant Ki for (14C)alpha-aminoisobutyric acid (AIB) was significantly increased by NS-1619 and minoxidil sulfate with respect to transport across the neovasculature forming the blood-**tumor** barrier but not with respect to transport across normal brain microvasculature. The results demonstrated that activation of potassium channels selectively increases the **permeability** of molecules across the capillaries of solid malignant **tumors** compared to capillaries supplying normal brain tissue.

USE - The method is used to treat mammals selected form humans, non-human primates, canine, feline, bovine, porcine, ovine, mouse, rat, gerbil, hamster or rabbit.

ADVANTAGE - The method provides increased selectivity of drug delivery to neoplastic tissue thereby minimizing damage to non-malignant tissue from e.g. **cytotoxic** chemotherapeutic agents. Selectivity is based on the role of calcium and ATP-dependent potassium transporters (channels) in mediating the **permeability** of microvasculature to drugs, macromolecules and viral particles combined with a greater number of calcium and ATP-dependent potassium channels present in abnormal brain vasculature or **tumor** neomicrovasculature compared to normal microvasculature.

Dwg.0/16

L24 ANSWER 3 OF 22 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 2001-343712 [36] WPIDS
DNC C2001-106466
TI Compound for stimulating an immune response against a **tumor** and for diagnosing or treating cancer, comprises effector agents and targeting ligands that bind receptors on the surface of a target cell or in the microenvironment of the cell.
DC B04 D16
IN GLAZIER, A

PA (DRUG-N) DRUG INNOVATION & DESIGN INC
CYC 94
PI WO 2001036003 A2 20010525 (200136)* EN 981p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001016075 A 20010530 (200152)
ADT WO 2001036003 A2 WO 2000-US31262 20001114; AU 2001016075 A AU 2001-16075 20001114
FDT AU 2001016075 A Based on WO 200136003
PRAI US 2000-241939 20001020; US 1999-165485 19991115; US 2000-239478 20001011
AB WO 200136003 A UPAB: 20010628
NOVELTY - A compound ET in which E is comprised of one or more effector agents having pharmacological activity designated as PA and T comprises a group referred to as a targeting ligand (TL) which selectively binds to a receptor (R) on the surface of the target cell (TC) or in the microenvironment of the TC, is new.

DETAILED DESCRIPTION - A new compound ET in which E is comprised of one or more effector agents having pharmacological activity designated as PA and T comprises:

(a) a group referred to as a targeting ligand (TL) which selectively binds to a receptor on the surface of the target cell (TC) or in the microenvironment of the target cell (TC); and

(b) one or more of:

(I) a TL which selectively binds to a target receptor (R) on the surface of the TC;

(II) a group, referred to as a masked intracellular ligand which can be modified in vivo to give a group referred to as an intracellular transport ligand which binds to R that actively transports bound ligands into the TC;

(III) a group referred to as a trigger that can be modified in vivo to activate the trigger and modulate the PA;

(IV) a group referred to as an intracellular trapping ligand which binds to one or more intracellular R's or a group referred to as a masked intracellular trapping ligand which can be modified in vivo to give an intracellular trapping ligand, where:

(i) a second targeting ligand is present in T allowing the ligands to bind simultaneously to two R's;

(ii) T consists of a TL and a trigger and when in vivo modification of the trigger increases the PA, the modification which activates the trigger is caused by an enzyme or enzymatic activity that is increased at TC or decreased at non-TC;

(iii) provided that T is not an antibody, an analog or component of an antibody, a complex of antibodies, a bispecific antibody, an analog of a bispecific antibody, a natural protein, a complex of natural proteins, a protein or natural occurring polymer, a radiolabelled dimer, or a polymer to which pharmacologically active compounds that evoke the same PA, are attached at multiple sites.

INDEPENDENT CLAIMS are also included for the following:

(1) a compound ET, where E is comprised of effector agents having PA and T is a targeting agent comprised of TL's or TL's and triggers, where:

(i) T increases PA to a TC compared to non-TC;

(ii) a TL is a group that selectively binds to a R;

(iii) a trigger is a group that upon in vivo modification by triggering agents becomes activated and modulates the activity of ET;

(iv) at the TC there are m different types of target molecules designated as (p1...pm), where one is present at increased amounts compared to a non-TC;

(v) the type of targeting molecule increased on the TC compared to a

non-TC, may be different for a different non-TC; and

(vi) ET can interact with (p1...pm), that is can bind to R or have the trigger modified by a triggering agent;

(2) a compound comprised of a masked intracellular transport ligand which can be modified in vivo to give an intracellular transport ligand which binds to R that actively transports bound ligands into the cell;

(3) delivering a targeted drug ET to a TC comprising contacting the TC with ET;

(4) stimulating an immune response against a **tumor** and treating a patient with cancer comprising:

(a) immunizing or sensitizing a patient to a compound referred to as a neoantigen; and

(b) administering to the a patient a neoantigen generating compound that can irreversibly chemically modify a component of the **tumor** resulting in the generation of the neoantigen at the **tumor**;

(5) a set of anticancer drugs referred to as E1T1 and E2T2 for use together or for co-administrating to a patient, where:

(a) E1 and E2 are effector agents that exhibit synergistic toxicity to a cell;

(b) T1 comprises a TL that binds to a R and T2 comprises a second TL that binds to a second R which is increased on a **tumor** cell compared to a normal cell and the first TL binds to a R that is a cathepsin type **protease**, a collagenase, a gelatinase, a matrix metalloproteinase, a membrane type matrix metalloproteinase, alpha v beta 3 integrin, bombesin/gastrin releasing peptide receptors, cathepsin B, D, K, L, or O, fibroblast activation protein, folate binding receptors, gastrin/cholecystokinin type B receptor, glutamate carboxypeptidase II or (PSMA), guanidinobenzoatase, laminin receptor, matrilysin, matripase, melanocyte stimulating hormone receptor, nitrobenzylthioinosine-binding receptors, norepenephrine transporters, nucleoside transporter proteins, peripheral benzodiazepam binding receptors, plasmin, seprase, sigma receptors, somatostatin receptors, stromelysin 3, trypsin, urokinase, MMP1, 2, 3, 7, 9, 12 or 13, or membrane type matrix mealloproteinase I; and

(6) a cancer diagnostic drug ET comprised of an effector group E that has effector agents that enable **tumor** imaging where T is comprised of:

(a) a **tumor** selective TL which selectively binds to a R that is increased on the surface of the **tumor** cell or in the microenvironment of the **tumor** cell compared to that for vital normal cells; and

(b) one or more of:

(I) a tumor selective TL;

(II) a masked intracellular transport ligand which can be modified in vivo to give an intracellular transport ligand which binds to an R that actively transports bound ligands into the tumor cell;

(III) a trigger that can be modified in vivo to activate the trigger and that increases the imaging signal at tumor cells or decreases the imaging signal intensity at nontumor cells; and

(IV) an intracellular trapping ligand which binds to intracellular R's or a masked intracellular trapping ligand which can be modified in vivo to give an intracellular trapping ligand; where T is comprised of a second TL, the TL's are able to bind simultaneously to two R's, and T is not an antibody, a complex of antibodies, a bispecific antibody, an analog of a bispecific antibody, a natural protein, a complex of natural proteins, a protein or natural occurring polymer, a radiolabelled dimer, or a polymer to which diagnostic imaging drugs are attached at multiple sites.

m = 2 - 20, preferably 2 - 6

ACTIVITY - Cytostatic; immunostimulatory.

MECHANISM OF ACTION - Selective cellular targeting.

USE - ET is used to stimulate an immune response against a tumor and treat a patient with cancer. It is also used as a cancer diagnostic drug

(claimed). ET is used for selective cellular targeting of a effector molecules.

ADVANTAGE - ET and methods using it enable selective delivery and/or selective activation of effector molecules to TC. It allows ultralow dose, multiple target, multiple drug chemotherapy, and targeted immunotherapy.

Dwg.0/0

L24 ANSWER 4 OF 22 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 2001-316134 [33] WPIDS
DNC C2001-097325
TI Culturing cells on semipermeable substrate, useful e.g. for growing hematopoietic cells for therapy, that is impermeable to proteins required for proliferation.
DC A96 B04 D16
IN NORDON, R E
PA (UNIX) UNISEARCH LTD
CYC 94
PI WO 2001023520 A1 20010405 (200133)* EN 39p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000078889 A 20010430 (200142)
ADT WO 2001023520 A1 WO 2000-AU1197 20000929; AU 2000078889 A AU 2000-78889 20000929
FDT AU 2000078889 A Based on WO 200123520
PRAI AU 1999-3191 19990930
AB WO 200123520 A UPAB: 20010615

NOVELTY - Culturing cells (A) of one or more types, comprising applying (A) to one side of a substrate (S) that is **permeable** to at least one nutrient, regulator or metabolite but impermeable to at least one protein (I) required for proliferation, differentiation and/or genetic modification of (A), is new.

DETAILED DESCRIPTION - Culturing cells (A) of one or more types, comprising applying (A) to one side of a substrate (S) that is **permeable** to at least one nutrient, regulator or metabolite but impermeable to at least one protein (I) required for proliferation, differentiation and/or genetic modification of (A), is new. The cells are contacted with medium containing at least one (I), and optionally at least one substance (II) required for proliferation. At least one (II) is provided on the acellular side of (S).

An INDEPENDENT CLAIM is also included for a bioreactor comprising many hollow fibers made of (S), placed within a housing that defines an acellular space through which a liquid flow is circulated.

ACTIVITY - Immunostimulant; hemostatic; antibacterial.

No biological data is given.

MECHANISM OF ACTION - None given.

USE - The method is used to prepare cells for therapeutic use, particularly neutrophil and platelet precursors for preventing neutropenia or thrombocytopenia following high-dose chemo/radiotherapy and hematopoietic stem cell transplant, hematopoietic cells, **cytotoxic** or antigen-specific T cells for immunotherapy of infections and malignant diseases, and cells transduced with gene therapy vectors. The method is also used for production of engineered proteins, **monoclonal** antibodies, cytokines, and viruses or for biosynthesis or degradation of compounds.

ADVANTAGE - The method allows cells to be grown and maintained at very high density, e.g. 40-50 times higher than that possible with conventional methods such as culture in T flasks.

Dwg.0/8

L24 ANSWER 5 OF 22 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 2001-245002 [25] WPIDS
DNC C2001-073571
TI New nucleic acid encoding a membrane type serine **protease**, useful for the diagnosis, prognosis and treatment of cancer, particularly metastatic cancers.
DC B04 D16
IN CRAIK, C S; SHUMAN, M; TAKEUCHI, T
PA (REGC) UNIV CALIFORNIA
CYC 93
PI WO 2001023524 A2 20010405 (200125)* EN 95p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2000079913 A 20010430 (200142)
ADT WO 2001023524 A2 WO 2000-US27250 20001002; AU 2000079913 A AU 2000-79913 20001002
FDT AU 2000079913 A Based on WO 200123524
PRAI US 1999-410362 19990930
AB WO 200123524 A UPAB: 20010508
NOVELTY - An isolated nucleic acid (I) encoding a serine **protease** domain (II), is new.
DETAILED DESCRIPTION - An isolated nucleic acid (I) comprising:
(a) a nucleic acid (NA) encoding a serine **protease** domain with a fully defined sequence (S1) of 895 amino acids (aa);
(b) a NA encoding a serine **protease** domain with the aa sequence of 615-855 of S1;
(c) a NA that specifically hybridizes to a NA with a fully defined sequence (S2) of 3121 base pairs (bp) or its fragments under stringent conditions and is of sufficient length that it can indicate the presence or absence of a NA encoding a membrane type serine **protease** (MT-SP) in a total genomic DNA pool, a total cDNA pool or a total mRNA pool sample from a PC-3 cell;
(d) a NA with the same sequence as a NA amplified from a PC-3 cDNA template using polymerase chain reaction (PCR) primers corresponding to nucleotides 37-54 of S2 and 2604-2583 of S2's complement;
(e) a DNA encoding an mRNA that when reverse transcribed produces the cDNA of S2 or produces the cDNA encoding aa 615-855 of S1;
(f) a pair of primers that when used in a NA amplification reaction with PC-3 cDNA template specifically amplifies a NA encoding the polypeptide (PP) of S1;
(g) a pair of primers that when used in a NA amplification reaction with mRNA template from a PC-3 cell specifically amplify a NA encoding the PP with the sequence of aa 615-855 of S1; and
(h) a NA encoding a MT-SP, which encodes a consensus sequence as defined in the specification and does not encode TRYB-human, ENTK-Human, HEPS-human, TRY2-Human and CTRB-human (all undefined).
INDEPENDENT CLAIMS are also included for the following:
(1) a PP:
(a) comprising a **protease** domain of S1;
(b) comprising a PP of S1;
(c) that has serine **protease** activity and is specifically bound by an antibody (Ab) raised against the PP of S1; and
(d) having **protease** activity and is 95% or more identical to a PP with the sequence of (aa 615-855 of) S1;
(2) detecting (M1) a cancer in an organism comprising detecting the level of a MT-SP1 in a biological sample, where an elevated level of MT-SP1 as compared to the level of the **protease** in a biological sample from a normal healthy organism indicates the presence of the

cancer;

(3) prescreening (M2) for a modulator of an MT-SP1 comprising contacting a NA encoding an MT-SP1 serine **protease** (protein) with a test agent and detecting specific binding of the test agent to the MT-SP1 protein or NA;

(4) an Ab (III) that binds specifically to MT-SP1;

(5) evaluating (M3) the severity or outcome of a cancer comprising measuring MT-SP1 in a biological sample from a cancer patient with at least a preliminary diagnosis of cancer and comparing the sample MT-SP1 level to the MT-SP1 level in normal healthy humans, where a sample MT-SP1 level in excess of MT-SP1 levels in normal healthy humans indicates a reduced survival expectancy compared to patients with normal MT-SP1 level;

(6) treating (M4) a cancer in a patient comprising carrying out M3 and selecting a patient identified with a MT-SP1 level in excess of MT-SP1 levels in normal healthy humans and providing an adjuvant therapy such as chemotherapy, radiation therapy, reoperation, antihormone therapy and immunotherapy;

(7) screening (M5) for recurrence of a cancer after removal of a primary **tumor** comprising measuring MT-SP1 in a biological sample from a cancer patient following removal of a primary **tumor** and comparing the sample MT-SP1 level to the MT-SP1 level in normal healthy humans, where a sample MT-SP1 level in excess of MT-SP1 levels in normal healthy humans indicates a possible recurrence of the cancer;

(8) monitoring (M6) effectiveness of cancer treatment in patients comprising measuring a level of MT-SP1 in a biological sample from a cancer patient during or after one or more treatments and comparing to the level of MT-SP1 in a biological sample taken from the patient prior to or following one or more cancer treatments, where a lower level of MT-SP1 in the second sample as compared to the MT-SP1 level in the first sample indicates efficacy in the one or more treatments;

(9) a chimeric molecule (IV) comprising an effector attached to (III); and

(10) specifically delivering (M7) an effector to a **tumor** cell expressing MT-SP1 comprising contacting the **tumor** with (IV).

ACTIVITY - Cytostatic. No supporting data is given.

MECHANISM OF ACTION - None given.

USE - MT-SP1 nucleic acids, polypeptides and antibodies are useful for the detection, evaluation of prognosis and/or screening for the recurrence of a cancer. (IV) is useful for the treatment of cancer by impairing the growth of **tumor** cells expressing MT-SP1 (claimed). A wide range of cancers can be diagnosed and/or treated such as gastric cancer, prostate cancer, cancers of the urinary tract, lung cancer, bronchus cancer, a colorectal cancer, breast cancer, pancreas cancer, brain or central nervous system cancer, peripheral nervous system cancer, esophageal cancer, cervical cancer, melanoma and kidney cancer etc. In particular it is suitable for metastatic cancers.

Dwg.0/6

L24 ANSWER 6 OF 22 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 2001-235264 [24] WPIDS
DNN N2001-168180 DNC C2001-070604
TI Composition comprising a PRO230, PRO216 or PRO302 polypeptide, agonist or antagonist for promoting or inhibiting angiogenesis and/or cardiovascularization in mammals.
DC B04 D16 S03
IN FONG, S; GERRITSEN, M E; GODDARD, A; GURNEY, A L; HILLAN, K J; WILLIAMS, P M; WOOD, W I
PA (GETH) GENENTECH INC
CYC 89
PI WO 2001019987 A1 20010322 (200124)* EN 141p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW

W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW

AU 2000017471 A 20010417 (200140)

ADT WO 2001019987 A1 WO 1999-US28214 19991129; AU 2000017471 A AU 2000-17471 19991129

FDT AU 2000017471 A Based on WO 200119987

PRAI WO 1999-US21090 19990915; WO 1999-US20944 19990913

AB WO 200119987 A UPAB: 20010502

NOVELTY - A composition (C1) comprising a PRO230, PRO216 or PRO302 polypeptide, agonist or antagonist for promoting or inhibiting angiogenesis and/or cardiovascularization in mammals, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a method of preparing C1, comprising admixing a PRO230, PRO216 or PRO302 polypeptide, agonist or antagonist;

(2) an article of manufacture comprising a container and a composition comprising a PRO230, PRO216 or PRO302 polypeptide, agonist or antagonist, where the agonist or antagonist are preferably an anti-PRO antibody;

(3) a method (M1) for identifying an agonist of a PRO230, PRO216 or PRO302 polypeptide;

(4) a method (M2) for identifying a compound capable of inhibiting the activity of a PRO230, PRO216 or PRO302 polypeptide;

(5) a method for identifying a compound that inhibits the expression of a PRO230, PRO216 or PRO302 polypeptide in cells that normally express the polypeptide;

(6) an agonist or antagonist of a PRO polypeptide;

(7) a compound, preferably an antisense oligonucleotide, that inhibits expression of a PRO230, PRO216 or PRO302 polypeptide;

(8) an isolated antibody that binds to a PRO230, PRO216 or PRO302 polypeptide;

(9) a method of diagnosing a disease or susceptibility to a disease related to a mutation in a PRO230, PRO216 or PRO302 polypeptide encoding nucleic acid;

(10) a method (M3) of diagnosing a cardiovascular, endothelial or angiogenic disorder in a mammal;

(11) a method for determining the presence of a PRO230, PRO216 or PRO302 polypeptide;

(12) a kit comprising an anti-PRO antibody;

(13) a method (M4) of treating a cardiovascular, endothelial or angiogenic disorder in a mammal;

(14) a recombinant retroviral particle comprising a retroviral vector consisting of a nucleic acid encoding a PRO230, PRO216 or PRO302 polypeptide, its agonist or antagonist polypeptide;

(15) an ex vivo producer cell comprising a nucleic acid construct that expresses retroviral structural proteins and the vector of (14), where the cell packages the vector in association with the structural proteins to produce recombinant retroviral particles;

(16) a method (M5) for stimulating or inhibiting cell growth in a mammal;

(17) a method for inhibiting or stimulating angiogenesis induced by a PRO302 polypeptide, comprising administering an anti-PRO302 antibody or PRO302 polypeptide, respectively;

(18) an isolated nucleic acid (N1) having at least 80% nucleic acid sequence identity to a nucleotide sequence that encodes one of the 3 polypeptide sequences (P1) defined in the specification;

(19) an isolated nucleic acid (N2) having at least 80% nucleic acid sequence identity to one of the 3 nucleotide sequences defined in the specification, where the defined sequences comprise a full-length coding sequence;

(20) an isolated nucleic acid (N3) having at least 80% nucleic acid

sequence identity to the full-length coding sequence of the DNA deposited under ATCC accession number 209264, 209381 or 209485;

(21) a vector comprising N1, N2 or N3;

(22) a host cell comprising the vector of (21);

(23) a process for producing a PRO230, PRO216 or PRO302 polypeptide, comprising culturing the host cell of (22);

(24) an isolated polypeptide (S1) having at least 80% sequence identity to an amino acid sequence selected from P1;

(25) an isolated polypeptide (S2) scoring at least 80% positives when compared to an amino acid sequence selected from P1;

(26) an isolated polypeptide (S3) having at least 80% sequence identity to an amino acid sequence encoded by the full-length coding sequence of the DNA deposited under ATCC accession number 209264, 209381 or 209485;

(27) a chimeric molecule comprising S1, S2 or S3 fused to a heterologous amino acid sequence;

(28) an antibody which specifically binds to S1, S2 or S3;

(29) isolated nucleic acid having at least 80% sequence identity to:

(a) a nucleotide sequence encoding a polypeptide selected from P1, where the polypeptide lacks its associated signal peptide; or

(b) a nucleotide sequence encoding an extracellular domain (ED) of a polypeptide selected from P1, where the polypeptide lacks or has its associated signal peptide; and

(30) an isolated polypeptide having at least 80% sequence identity to:

(a) a polypeptide selected from P1, where the polypeptide lacks its associated signal peptide; or

(b) an ED of a polypeptide selected from P1, where the polypeptide lacks or has its associated signal peptide.

ACTIVITY - Cardiant; antiangiogenic; antiarteriosclerotic; hypotensive; antirheumatic; antiarthritic; antiinflammatory; cytostatic.

Hairless guinea pigs (350 grams or more) were anesthetized with Ketamine (75-80 mg/kg) and 5 mg/kg Xylazine intramuscularly. Test samples containing a PRO302 polypeptide or a physiological buffer without the test polypeptide were injected into skin on the back of the test animals with 100 microlitres per injection site intradermally. There were approximately 16-24 injection sites per animal. One ml of Evans blue dye (1% in phosphate buffered saline) was then injected intracardially. Skin vascular permeability responses to the compounds (i.e., blemishes at the injection sites of injection) were visually scored by measuring the diameter (in mm) of blue-colored leaks from the injection site at 1 and 6 hours post administration of the test materials. The diameter of blueness at the injection site was observed and recorded as well as the severity of the vascular leakage. Blemishes of at least 5 mm in diameter were considered positive for the assay when testing purified proteins, being indicative of the ability to induce vascular leakage or permeability. A response greater than 7 mm diameter was considered positive for conditioned media samples. Human vascular endothelial growth factor at 0.1 micrograms/100 microlitres was used as a positive control, inducing a response of 15-23 mm diameter. At both 1 and 6 hours post-injection, the PRO302 polypeptide induced a response of 9 mm diameter.

MECHANISM OF ACTION - Gene therapy.

USE - The PRO nucleic acids, polypeptides, agonists and antagonists are useful for treating or diagnosing a cardiovascular, endothelial or angiogenic disorder in a mammal, e.g. cardiac hypertrophy, trauma, cancer, age-related macular degeneration, atherosclerosis, hypertension, arterial restenosis, rheumatoid arthritis, angina, myocardial infarctions, thrombophlebitis and lymphangitis. The PRO polypeptide and antagonists are also used to prevent tumor angiogenesis and for treating periodontal diseases.

Dwg.0/6

AN 2001-138319 [14] WPIDS
DNC C2001-040811
TI Novel antagonist inhibiting angiogenesis by modifying protein-protein interactions, specifically matrix metalloprotease-9 - beta1 containing integrin interaction, useful to inhibit psoriasis, macular degeneration.
DC B04 D16
IN BROOKS, P C; HASSANIEH, L; RODRIGUEZ, D
PA (UYSC-N) UNIV SOUTHERN CALIFORNIA
CYC 93
PI WO 2001004157 A2 20010118 (200114)* EN 62p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2000063447 A 20010130 (200127)
ADT WO 2001004157 A2 WO 2000-US19095 20000713; AU 2000063447 A AU 2000-63447 20000713
FDT AU 2000063447 A Based on WO 200104157
PRAI US 1999-152495 19990902; US 1999-143581 19990713
AB WO 200104157 A UPAB: 20010312
NOVELTY - An antagonist (I) that inhibits angiogenesis by modifying protein-protein interactions, is new. The interactions comprise interactions between two polypeptides with different sequences.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a polypeptide (II) for inhibiting angiogenesis and/or **tumor** growth, which specifically binds to matrix metalloprotease (MMP)-9 with a binding affinity greater than the binding capacity of CysArgAlaAlaAlaAlaGluProGlyCys (S3) to MMP-9;

(2) a polypeptide (III) for inhibiting angiogenesis or **tumor** growth, which specifically binds to a beta 1 containing integrin with a binding affinity greater than the binding affinity of (S3) to the integrin;

(3) an antagonist (IV) that specifically binds with CysArgLeuArgSerGlyGluProGlnCys (S1) but binds to (S3) with substantially reduced affinity and which disrupts the localization of MMP-9 on a cell surface or blood vessel;

(4) screening (M1) for MMP-9 or beta 1 integrin antagonists, comprising:

(a) providing a putative antagonist;

(b) measuring the putative antagonist's affinity for binding with MMP-9 or beta 1 integrin;

(c) measuring a second affinity of (S3) for binding with MMP-9 or beta 1 integrin; and

(d) selecting the putative antagonist as an MMP-9 or beta 1 integrin antagonist if the second affinity is less than the first; and

(5) a peptide (V) comprising a sequence encoding an epitope recognized by (I).

ACTIVITY - Cytostatic; antitumor; antipsoriatic; vasotropic; antidiabetic; osteopathic; anti-rheumatoid; antiarthritic; antiatherosclerotic; ophthalmological; antiinflammatory.

MECHANISM OF ACTION - Interaction between MMP-9 and B1 integrin antagonist; angiogenesis inhibitor.

The biological activity of (I) was tested in vitro. CS-1 melanoma cells were inoculated on the CAMs (cell adhesion molecules) of 10 day old chick embryos. Twenty four hours later, the embryos received a single intravenous injection of purified Mab (**monoclonal** antibody) FM155. After 7 days **tumors** were resected and wet weight determined. Results showed that Mab FM155 potently inhibited CS-1 melanoma **tumor** growth in vivo. These findings indicate that the blocking of the interactions of MMP-9 and alpha 5 beta 1 may play a significant role

in regulating angiogenesis and **tumor** growth in vivo.

USE - (I) inhibits angiogenesis, **tumor** growth, metastasis, or a disease state such as psoriasis, macular degeneration, neurological disease, or restenosis in a tissue. (I) is useful for inhibiting angiogenesis, in a mammalian arthritic, ocular, retinal, or hemangioma tissue which is inflamed and angiogenesis is occurring. (I) is also useful for inhibiting **tumor** growth or metastasis such as melanoma, **carcinoma**, **sarcoma**, fibrosarcoma, glioma, or astrocytoma, in a tissue. (I) is also useful for inhibiting psoriasis, macular degeneration or restenosis in a tissue. In all the above conditions, (I) is administered in conjunction with chemotherapy or radiation. (I) is also useful for detecting angiogenesis and detecting **tumors** or **tumor** invasion in a tissue ex vivo. The antagonist in this case is conjugated to fluorochrome, radioactive tag, paramagnetic heavy metal, diagnostic dye or enzyme. (All claimed). (I) is also useful for treating diabetic retinopathy, neovascular glaucoma, atherosclerotic plaques, osteoporosis, rheumatoid arthritis and other inflammatory diseases.

ADVANTAGE - The method are effective in part because the therapy is highly selective for angiogenesis and no other biological processes. Only new vessel growth is inhibited by antagonists that disrupt the localization of MMP-9, and therefore the therapeutic methods do not adversely effect mature vessels. Also, because certain of (I) affect only the localization of MMP-9, and do not directly block the **proteolytic** activity of MMP-9 or the adhesive functions of the beta 1 integrins, it is likely that these compounds will have fewer side effects because the **proteolytic** activity of MMP-9 or the adhesive functions of the beta 1 integrins may have normal physiological functions. The antagonists are highly potent suggesting that they may have therapeutic benefits at low concentrations.

DESCRIPTION OF DRAWING(S) - The figure shows the results of the purification of beta 1 integrin, alpha 5 beta 1 from placental lysates using 110 kDa cell binding domain of fibronectin.

Dwg.1/11

L24 ANSWER 8 OF 22 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 2000-687068 [67] WPIDS
DNN N2000-508003 DNC C2000-208995
TI Use of ubiquitin cross-reactive protein, e.g., diubiquitin, as a marker for identifying malignant cells or cells with increased sensitivity to **cytotoxic** agents such as camptothecin.
DC B04 D16 S03
IN DESAI, S D; LAVOIE, E J; LIU, L F
PA (RUTF) UNIV RUTGERS STATE NEW JERSEY
CYC 92
PI WO 2000062075 A1 20001019 (200067)* EN 43p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000043475 A 20001114 (200108)
ADT WO 2000062075 A1 WO 2000-US9959 20000413; AU 2000043475 A AU 2000-43475 20000413
FDT AU 2000043475 A Based on WO 200062075
PRAI US 1999-157745 19991005; US 1999-129063 19990413
AB WO 200062075 A UPAB: 20001223
NOVELTY - Ubiquitin cross-reactive protein (UCRP) is used as a marker for identifying cells sensitive to DNA-damaging agents, identifying cells which have a defective ubiquitin/proteasome **proteolytic** processing pathway, or for distinguishing benign **tumor** cells from malignant **tumor** cells.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(A) identification of cells sensitive to DNA-damaging agents, comprising determining the relative level of a cellular UCRP, where an elevated level of the UCRP is indicative of increased sensitivity;

(B) identification of cells which have a defective ubiquitin/proteasome **proteolytic** processing pathway, comprising determining the presence of a cellular UCRP in the cells, where the presence of the UCRP correlates with a defective ubiquitin/proteasome **proteolytic** processing pathway; and

(C) distinguishing benign **tumor** cells from malignant **tumor** cells, comprising determining the relative level of cellular UCRP in a preselected sample of a **tumor**, where an elevated level of cellular UCRP is indicative of a malignant **tumor**.

ACTIVITY - Cytostatic.

MECHANISM OF ACTION - Topoisomerase I inhibitor; topoisomerase II inhibitor.

USE - The processes are useful in treatment of cancers, in determining improved methods for treatment of cancers, and in distinguishing malignant **tumor** cells from benign **tumor** cells.

ADVANTAGE - Process (A) provides a prognostic marker (for the relative level of cellular UCRP) for the identification of cancers in which DNA-damaging agents are more likely to provide effective treatment. Process (C) allows malignant **tumor** cells to be distinguished from benign **tumor** cells, using UCRP as a marker for the malignant state. Process (B) allows detection of cells with abnormal ubiquitin-associated **proteolytic** degradation processes, which can be useful in both clinical practice and laboratory research.

DESCRIPTION OF DRAWING(S) - The diagram shows a western blot analysis of topoisomerase (top)I (A), a western blot analysis of a topI-small ubiquitin modifiers-I (SUMO-) conjugate (B), an immunoblot analysis of levels of topI remaining in cells treated with camptothecin (C) and a western blot of to levels of top2 alpha in cells treated with camptothecin (D).

Dwg.1/9

L24 ANSWER 9 OF 22 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 2000-531471 [48] WPIDS
CR 1993-303150 [38]; 1996-097460 [10]; 1997-434333 [40]; 1998-397937 [34]; 1999-105025 [09]; 1999-131255 [11]; 1999-189722 [16]; 1999-579890 [49]; 2000-072047 [06]; 2000-269871 [22]; 2000-363766 [28]; 2001-450473 [48]
DNC C2000-158393
TI New immunological and growth factor-based bispecific binding ligands, useful for stimulating coagulation in vasculature-associated diseases, e.g. for treating both benign and malignant diseases (e.g. meningioma or hemangioma).
DC B04 D16
IN EDGINGTON, T S; THORPE, P E
PA (SCRI) SCRIPPS RES INST; (TEXA) UNIV TEXAS SYSTEM
CYC 1
PI US 6093399 A 20000725 (200048)* 83p
ADT US 6093399 A CIP of US 1992-846349 19920305, CIP of US 1994-205330 19940302, CIP of US 1994-273567 19940711, US 1995-482369 19950607
PRAI US 1995-482369 19950607; US 1992-846349 19920305; US 1994-205330 19940302; US 1994-273567 19940711
AB US 6093399 A UPAB: 20010829
NOVELTY - A binding ligand (I) comprising a first binding region that is operatively linked to a coagulation factor, or a second binding region that binds to a coagulation factor, is new.

DETAILED DESCRIPTION - A binding ligand (I) comprising a first binding region that binds to a component expressed, accessible to binding or localized on the surface of a **tumor** cell, intratumoral

vasculature or **tumor** stroma, is new. The first binding region is operatively linked to a coagulation factor, or a second binding region that binds to a coagulation factor. The second binding region comprises an antibody or an antigen binding region of an antibody.

INDEPENDENT CLAIMS are also included for the following:

(1) a binding ligand comprising a first binding region that binds to a component expressed, accessible to binding or localized on the surface of intratumoral vasculature or stroma, where the first binding region is operatively linked to a coagulant or an antibody, or an antigen binding region that binds to a coagulant;

(2) a binding ligand comprising a first antibody or its antigen binding region, which binds to a component expressed, accessible to binding or localized on the surface of intratumoral vasculature or stroma, where the first antibody or antigen binding region is operatively linked to a coagulant or to a second antibody, or antigen binding region that binds to a coagulant;

(3) binding ligands comprising a first antibody or its antigen binding region, which binds to a marker expressed, accessible to binding or localized on the cell surface of intratumoral blood vessels of a vascularized **tumor**, where the first antibody or antigen binding region is linked to a coagulant or to a second antibody, or its antigen binding region that binds to a coagulant;

(4) a conjugate comprising a first antibody or its antigen binding portion that binds to a marker expressed or localized on the cell surface of intratumoral blood vessels of a vascularized **tumor**, where the first antibody or antigen binding portion is linked to a coagulant or a second antibody, or an antigen binding region that binds to a coagulant;

(5) binding ligands comprising a first binding region that binds to a component expressed, accessible to binding or localized on the surface of a **tumor** cell, established intratumoral vasculature, **tumor**-associated vasculature or **tumor** stroma, where the first binding region is operatively linked to a coagulation factor or to an antibody or its antigen binding region that binds to a coagulation factor; and

(6) a pharmaceutical composition comprising (I).

ACTIVITY - Cytostatic; coagulant. A20 cells coated with B21-2/10H10 complex and truncated Tissue Factor (tTF) were capable of inducing fibrin formation, it shortened coagulation time from 140 seconds (the time for mouse plasma in CaCl2 to coagulate in the absence of added antibodies or TF under specific conditions) to 60 seconds. Mouse plasma added to A20 cells to which tTF had been tethered with B21-2/10H10 coagulated rapidly. Fibrin strands were visible 36 seconds after addition of plasma as compared with 164 seconds in plasma added to untreated A20 cells.

MECHANISM OF ACTION - Thrombin stimulator. For establishment of solid **tumors**, 1.5 multiply 107 C1300 cells were injected subcutaneously into the right anterior flank of BALB/c nu/nu mice. When **tumors** had grown to 0.8 cm in diameter, mice were randomly assigned to treatment groups each containing 7-8 mice. Mice 0.8 cm diameter **tumors** administered with the coaguligand, composed of B21-2/10H10 and tTF, showed **tumor** regression to approximately half their pre-treatment size. Repeated treatment on the 7th day caused the **tumors** to regress further, usually completely. In 5/7 animals, complete regressions were obtained. These anti-**tumor** effects were statistically highly significant (P is less than 0.001) when compared with all other groups.

USE - The binding ligand is useful for effectively promoting coagulation in intratumoral blood vessels when administered to a subject having vascularized **tumor** (claimed). It is useful in achieving specific coagulation , e.g. coagulation in **tumor** vasculature. Furthermore, the binding ligand is useful for stimulating coagulation in vasculature-associated diseases. Particularly, the binding ligand is useful for treating both benign and malignant diseases that have a vascular component. These diseases include benign growths (e.g. BPH), diabetic retinopathy, arteriovenous malformations, meningioma, hemangioma,

neovascular glaucoma, psoriasis, synovitis, endometriosis, hemophylic joints, hypertrophic scars or vascular adhesions. The binding ligands may also be combined with anti-**tumor** therapy (e.g. radiotherapy or chemotherapy).

ADVANTAGE - **Immunotoxins** have proven effective at treating lymphomas and leukemias. However, **immunotoxins** are ineffective in the treatment of solid **tumors**. Another problem is that antigen-deficient mutants can escape being killed by the **immunotoxin** and regrow. The present binding ligands offer several advantages. Firstly, the target cells are directly accessible to intravenously administered ligands, permitting rapid localization of high percentage of the injected dose. Secondly, since each capillary provides oxygen and nutrients for thousands of cells in its surrounding cord of **tumor**, even limited **damage** to the **tumor** vasculature could produce an avalanche of **tumor** cell death. Finally, the outgrowth of mutant endothelial cells, lacking a target antigen, is unlikely because they are normal cells. Thus, the binding ligands are safer for use in humans than that of targeting a toxin to **tumor** vasculature.

Dwg.0/8

L24 ANSWER 10 OF 22 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 2000-376495 [32] WPIDS
DNC C2000-113897
TI Novel polynucleotides encoding a novel growth factor of cells expressing a platelet-derived growth factor, useful for diagnostic and therapeutic applications, e.g. concerning cancer.
DC B04 D16
IN AASE, K; ALITALO, K; ERIKSSON, U; HELDIN, C; LI, X; OESTMAN, A; PONTEN, A; UUTELA, M; LEE, X
PA (LUDW-N) LUDWIG INST CANCER RES; (UYHE-N) UNIV HELSINKI LICENSING LTD OY; (LICE-N) LICENTIA LTD
CYC 76
PI WO 2000027879 A1 20000518 (200032)* EN 111p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AU BA BB BG BR CA CN CU CZ EE GD HR HU ID IL IN IS JP KP KR LC LK LR LT LV MG MK MN MX NO NZ PL RO SG SI SK TR TT UA UZ VN YU
AU 2000016136 A 20000529 (200041)
EP 1129110 A1 20010905 (200151) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
ADT WO 2000027879 A1 WO 1999-US26462 19991110; AU 2000016136 A AU 2000-16136 19991110; EP 1129110 A1 EP 1999-958854 19991110, WO 1999-US26462 19991110
FDT AU 2000016136 A Based on WO 200027879; EP 1129110 A1 Based on WO 200027879
PRAI US 1999-157756 19991005; US 1998-107852 19981110; US 1998-113997 19981228; US 1999-150604 19990826; US 1999-157108 19991004
AB WO 200027879 A UPAB: 20000706
NOVELTY - Polynucleotide (I) encoding a novel growth factor (II) of cells expressing a platelet-derived growth factor, comprising a sequence with at least 85 % identity to nucleotides 1-600 of a sequence of 690 base pairs (bp; s1), nucleotides 1-966 or 176-1288 of a sequence of 1934 bp (s2) or nucleotides 938-1288 of a sequence of 2253 bp (s3), all given in the specification, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) an isolated polypeptide (II) encoded by (I), with at least 85 % identity to a 200 (s4), 322 (s5) or 370 (s6) amino acid (aa) sequence given in the specification;

(2) a vector (III) comprising (I);

(3) producing (III) expressing (II) comprising incorporating (I) into a vector in operatively linked relation with the promoter;

(4) producing a vector expressing a polypeptide with at least 85 %

identity to residues 255-371 of s6 comprising incorporating nucleic acid encoding the amino acid residues into a suitable vector in operatively linked relation with the promoter;

(5) a host cell comprising (III);

(6) pharmaceutical composition comprising (II);

(7) amplifying (I) comprising utilizing a pair of primers complementary to (I);

(8) an antibody specific to (II);

(9) preparation of (II);

(10) producing an activated truncated form of PDGF-D comprising expressing (III) and supplying **proteolytic** amount of an enzyme for processing the expressed (II) to generate the activated truncated form of PDGF-D;

(11) an isolated polypeptide dimer comprising (II);

(12) identifying specific types of human **tumors** comprising testing a sample of **tumor** for the expression PDGF-D; and

(13) identifying a PDGF-D antagonist comprising mixing activated truncated form and full length PDGF-D with a test agent and monitoring the inhibition in biological activity of PDGF-D and cleavage of CUB domain from PDGF-D respectively.

ACTIVITY - Cytostatic; vulnerary; antiathersclrotic; proliferative.

MECHANISM OF ACTION - Activator of differentiation growth and motility of cells expressing PDGF-D receptor (claimed). No supporting data is given.

USE - (II) is useful for stimulating and/or enhancing proliferation and/or differentiation and/or growth and/or motility of cells preferably endothelial cells, connective tissue cells, myofibroblast cells and glial cells expressing PDGF-D receptor (beta receptor). (II) is also useful for inhibiting the growth of **tumors** expressing PDGF-D in a mammal (all claimed). Expression of (III) and **proteolytic** cleavage for generating an activated truncated form is useful for regulating receptor binding specificity of PDGF-D (claimed). PDGF-C antagonist is useful for inhibiting tissue remodeling during the invasion of **tumor** cells into normal cells (claimed). Vectors comprising antisense nucleotides are useful for inhibiting PDGF-D expression. PDGF-D may be used to treat wounds, atherosclerosis, metastasis, and the migration of smooth muscle cells.

Dwg.0/13

L24 ANSWER 11 OF 22 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 2000-350295 [30] WPIDS
DNC C2000-106478
TI Compositions comprising a biologically active agent encapsulated by a carboxylic acid, useful for the oral delivery of pharmaceutical agents.
DC B05 C02 C03 D16
IN RUSSELL-JONES, G J
PA (BIOT-N) BIOTECH AUSTRALIA PTY LTD
CYC 89
PI WO 2000022909 A2 20000427 (200030)* EN 31p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2000010712 A 20000508 (200037)
ADT WO 2000022909 A2 WO 1999-IB1872 19991018; AU 2000010712 A AU 2000-10712 19991018
FDT AU 2000010712 A Based on WO 200022909
PRAI US 1998-104827 19981019
AB WO 200022909 A UPAB: 20000624
NOVELTY - A novel pharmaceutical composition comprises a biologically active agent encapsulated by a carboxylic acid that forms a complex that

is stable at an acidic pH in solution and unstable at a basic pH in solution, where the carboxylic acid does not have an amide bond or a non-aromatic nitrogen.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a method for the preparation of a pharmaceutical composition comprising:

(a) selecting a biologically active carboxylic acid that forms a complex which is stable at an acidic pH in solution and unstable at a basic pH in solution;

(b) dissolving the biologically active carboxylic acid in an alcohol;

(c) adding the mixture to a suitably basic solution in which the acid is soluble; and

(d) adding the solution containing mixture to an acidic solution and stirring such that the carboxylic acid precipitates.

USE - The compositions can be used for the delivery of pharmaceutical agents which otherwise would experience a loss of efficacy as a result of instability, inadequate uptake following oral administration, inappropriate rate of release, and/or insufficient solubility. They can be used for therapy, prophylaxis or diagnosis in e.g. humans, domestic animals, farm animals or wild animals.

ADVANTAGE - The compositions provide improved methods of protecting pharmaceuticals from intestinal degradation, for enhancing the oral uptake of the pharmaceutical agent within a vertebrate host and for the delivery of insoluble and moderately soluble pharmaceutical agents, and biologically active pharmaceutical agents.

Dwg.0/2

L24 ANSWER 12 OF 22 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1999-540586 [45] WPIDS
DNN N1999-400666 DNC C1999-157881
TI New peptides containing at least one epitope from Tek receptor tyrosine kinase, used in vaccines against cancer.
DC B04 D16 S03
IN DURRANT, L G; HEWETT, P W; RAMAGE, J M; SPENDLOVE, I
PA (CANC-N) CANCER RES CAMPAIGN TECHNOLOGY
CYC 85
PI WO 9943801 A1 19990902 (199945)* EN 56p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
AU 9926331 A 19990915 (200004)
EP 1056852 A1 20001206 (200064) EN
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
ADT WO 9943801 A1 WO 1999-GB583 19990226; AU 9926331 A AU 1999-26331 19990226; EP 1056852 A1 EP 1999-906368 19990226, WO 1999-GB583 19990226
FDT AU 9926331 A Based on WO 9943801; EP 1056852 A1 Based on WO 9943801
PRAI GB 1998-4121 19980226
AB WO 9943801 A UPAB: 19991103
NOVELTY - Peptide (I):

(a) comprises less than the full-length sequence of Tek (a receptor tyrosine kinase);

(b) consists of one or more Tek epitopes, and

(c) binds to major histocompatibility complex (MHC) molecules to stimulate an immune response.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(a) polypeptide (II) comprising (I) plus at least one sequence not characteristic of Tek;

(b) antibodies (Ab) that bind to (I) or (II), and their fragments, derivatives, functional equivalents or homologs;

(c) cells cultures that produce Ab or their fragments;

(d) nucleic acid (III) that encodes Ab or its fragments;
(e) recombinant DNA construct or virus vector containing a nucleic acid (IV) that encodes (I) or (II);
(f) host cells able to express (IV);
(g) recombinant production of Ab or their fragments by growing cells of (c);
(h) vaccine for targeting endothelial cells (EC) lining the blood vessels of a **tumor** comprising (I), (II) or the constructs/vectors of (e);
(i) (IV);
(j) recombinant production of (I) or (II) by expressing (IV);
(k) vector containing (IV); and
(l) host cell containing the vector of (k).
ACTIVITY - Anticancer; anti-angiogenic.
MECHANISM OF ACTION - (I) bind to MHC and the presence of T cell epitopes stimulates helper cell and/or **cytotoxic** T cell responses. The immune response is directed against endothelial cells (EC) in the **tumor**-associated vasculature and includes production of antibodies that bind to the cells, causing coagulation and thrombosis. The peptide that had the highest stabilization ratio on HLA-A2, i.e. LMNQHQDPL, was tested at 20 mg/ml for stimulating proliferation of T cells from peripheral blood mononuclear cells, by measurement of incorporation of tritiated thymidine . For a subject of haplotype HLA-DR 1,4, the highest response was after 9 days and was (in counts/min) 3197 compared with 447 for controls. The peptide ITIGRDFEALMNQHQDPLEV, containing two T-cell epitopes, induced proliferation in all cell donors tested.
USE - (I), and its fusion proteins (II), are used:
(1) to generate antibodies (Ab) reactive with epitopes present in wild-type Tek, and
(2) for prevention and treatment of cancer.
(I) and (II), also recombinant DNA constructs or viral vectors that express them, are useful as anticancer vaccines to target endothelial cells (EC) that line blood vessels of the **tumor**. Nucleic acid (IV) encoding (I) are used for expression of recombinant (I); as source of probes, and to generate transgenic anmals. Ab are used to isolate or purify (I).
ADVANTAGE - The immune response is targeted to EC lining blood vessels of the **tumor** (these cells overexpress Tek), so **damage** to even a few EC will kill many **tumor** cells. These target cells are accessible to the immune response and problems of antigenic heterogeneity, MHC loss and resistance to apoptosis (associated with epithelial cells) are unlikely to occur in normal EC.
Dwg.0/5

L24 ANSWER 13 OF 22 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1999-430394 [36] WPIDS
CR 1999-590729 [42]
DNN N1999-320416 DNC C1999-126860
TI New isolated apoptosis inducing molecule II polypeptides.
DC B04 C07 D16 S03
IN EBNER, R; RUBEN, S M; ULLRICH, S; YU, G
PA (HUMA-N) HUMAN GENOME SCI INC; (EBNE-I) EBNER R; (RUBE-I) RUBEN S M; (ULLR-I) ULLRICH S; (YUGG-I) YU G; (ZHAI-I) ZHAI Y; (ZHAN-I) ZHANG
CYC 84
PI WO 9935262 A2 19990715 (199936)* EN 164p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW
AU 9921063 A 19990726 (199952)
AU 9929721 A 19990906 (200003)

EP 1044270 A2 20001018 (200053) EN
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
ADT WO 9935262 A2 WO 1999-US242 19990107; AU 9921063 A AU 1999-21063 19990107; AU 9929721 A AU 1999-29721 19990219; EP 1044270 A2 EP 1999-901341 19990107, WO 1999-US242 19990107
FDT AU 9921063 A Based on WO 9935262; AU 9929721 A Based on WO 9942584; EP 1044270 A2 Based on WO 9935262
PRAI US 1998-27287 19980220; US 1998-3886 19980107; US 1998-75409 19980220
AB WO 9935262 A UPAB: 20001023
NOVELTY - Isolated apoptosis inducing molecule II (AIM II) polypeptides and nucleic acids, are new.

DETAILED DESCRIPTION - (A) A novel isolated polypeptide comprises a member selected from:

(a) an apoptosis inducing molecule (II) (AIM II) N-terminal deletion mutant which has the amino acid sequence shown in sequence (II) (240 amino acids in length), provided that the amino acid sequence has a deletion of at least the first N-terminal amino acid residue but not more than the first 114 N-terminal amino acid residues of sequence (II);

(b) a polypeptide having an amino acid sequence at least 95% identical to an amino acid sequence identical to (a); and

(c) a polypeptide having an amino acid sequence identical to that of (a) except for at least one amino acid substitution.

INDEPENDENT CLAIMS are also included for the following:

(1) an isolated polynucleotide (PN) 1169 bp (sequence given in the specification), encoding a polypeptide as in (A);

(2) a vector, and its method of production;

(3) a recombinant host cell and its method of production comprising introducing a recombinant vector as in (3) into a host cell;

(4) an isolated nucleic acid molecule (NAM) comprising a nucleotide sequence (NS) at least 95% identical to a sequence selected from:

(a) a NS encoding amino acids from 1 to 240 or 2 to 240 of sequence (II);

(b) a NS encoding an amino acid sequence encoded by a cDNA clone contained in ATCC No. 97689 or 97483;

(c) a NS encoding an AIM II polypeptide transmembrane domain, polypeptide intracellular domain or polypeptide having extracellular and intracellular domains but lacking the transmembrane domain; and

(d) a NS complementary to any of the NSs above;

(5) an isolated NAM comprising a PN which encodes an amino acid sequence of an epitope-bearing portion of an AIM II polypeptide as in sequence (II);

(6) (8) an isolated NAM selected from:

(a) at least 20 contiguous nucleotides of sequence (I) (1169 nucleotides in length), provided that the isolated NAM is not sequence (XX) (503 nucleotides in length) or any subfragments;

(b) a NS complementary to a NS as in (a); and

(c) (c) a NAM at least 20 nucleotides in length that hybridizes under stringent hybridization conditions to a NAM having a NS shown in sequence (I);

(7) an isolated AIM II polypeptide comprising an amino acid sequence at least 95% identical to a sequence selected from:

(a) amino acids from 1 to 240 or 2 to 240 in sequence (II);

(b) an amino acid sequence encoded by a cDNA clone contained in ATCC 97689 or 97483;

(c) an amino acid sequence of an extracellular domain, transmembrane domain or intracellular domain of the AIM II polypeptide;

(d) an amino acid sequence of a soluble AIM II polypeptide having all or part of the extracellular and intracellular domain but lacking the transmembrane domain; and

(e) the amino acid sequence of an epitope-bearing portion of any one of the polypeptides above;

(8) an AIM II polypeptide selected from a polypeptide comprising

amino acid residues from 13 to 20, 23 to 36, 69 to 79, 85 to 94, 167 to 178, 184 to 196 or 221 to 233 in sequence (II);

(9) a method for making a recombinant vector comprising inserting an isolated NAM as in (4) into a vector;

(10) a recombinant vector produced by a method as in (9);

(11) a method of making a recombinant host cell comprising introducing a recombinant vector as in (10) into a host cell; and

(12) a recombinant host cell produced by a method as in (11).

ACTIVITY - Antiallergic; antiinflammatory; immunomodulator; antidiabetic; antibacterial; immunosuppressive; neuroprotective; osteopathic; antirheumatic; antiarthritic; dermatological.

MECHANISM OF ACTION - The effects of AIM II transduction on tumor growth were evaluated in vivo. When MDA-MB-231 cells were inoculated into mammary fat pads, AIM II expression significantly inhibited tumor formation of MDA-MB-231 in nude mice, whereas the vector control MDA-MB-231/Neo cells showed no change in tumor growth as compared with that of the parental MDA-MB-231 cells. Similar tumor suppression in the MDA-MB-231/AIM II cells was also demonstrated in SCID mice. A histological examination of the tumors from AIM II expressing MDA-MB-231 cells or those from parental or vector control cells was performed. Parental or vector control MDA-MB-231 cells formed a large solid tumor mass filled with predominantly tumor cells with little or no cellular infiltrates.

In contrast, there was extensive necrosis observed even in small residual tumors formed by the MDA-MB-231/AIM II cells in nude mice. Furthermore, in AIM II expressing tumors, there is a significant increase in number of infiltrating neutrophil cells. The average number of neutrophils per mm2 tumor size in wild type, Neo control, and AIM II transduced MDA-MB-231 tumors were 101 plus or minus 26, 77 plus or minus 16, and 226 plus or minus 38 respectively, based on the immunohistological staining using Gr-1 monoclonal antibody. The inhibitory effect of AIM II on tumor suppression was further validated in the syngeneic murine tumor model. Local expression of AIM II in MC-38 murine colon cancer cells resulted in complete suppression of tumor formation in 8 out of 10 C57BL/6 mice. Local production of AMI II also dramatically prolonged the survival of mice bearing MC-38 tumors.

USE - The AIM II polypeptides mediate apoptosis by stimulating clonal deletion of T-cells. They can be used to treat lymphoproliferative disease which results in lymphoadenopathy, to stimulate peripheral tolerance and cytotoxic T-cell mediated apoptosis. They can be used to stimulate peripheral tolerance, destroy some transformed cell lines, mediate cell activation and proliferation and are functionally linked as primary mediators of immune regulation and inflammatory response. They can be used to treat autoimmune disease e.g. systemic lupus erythematosis (SLE), immunoproliferative disease lymphadenopathy (IPL), angioimmunoproliferative lymphadenopathy (AIL), immunoblastive lymphadenopathy (IBL), diabetes, multiple sclerosis, allergies, graft versus host disease.

Antagonists to AIM II polypeptides may be used to treat cachexia which is a lipid clearing defect resulting from a systemic deficiency of lipoprotein lipase, which is believed to be suppressed by AIM II, to treat cerebral malaria in which AIM II may play a pathogenic role, to treat rheumatoid arthritis by inhibiting AIM II induced production of inflammatory cytokines, such as IL-1 in the synovial cells, to prevent graft-versus-host rejection by preventing the stimulation of the immune system in the presence of a graft, to inhibit bone resorption and therefore to treat and/or prevent osteoporosis. They can also be used as anti-inflammatory agents, to treat endotoxic shock, and prevent activation of the HIV virus. The products can also be used for detection, diagnosis and prognosis. They can be used in mammals e.g. monkeys, apes, cats, dogs, cows, pigs, horses, rabbits and humans.

Dwg.0/2

L24 ANSWER 14 OF 22 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD

AN 1999-403898 [34] WPIDS
DNN N1999-300978 DNC C1999-119143
TI Treatment of **tumors** communicating with arterial and venous blood with minimal drug diffusion to body.
DC B07 D16 K08 P31 S03 S05 T01
IN LEMELSON, J
PA (LEME-I) LEMELSON J
CYC 1
PI US 5919135 A 19990706 (199934)* 14p
ADT US 5919135 A US 1997-807646 19970228
PRAI US 1997-807646 19970228
AB US 5919135 A UPAB: 19990825
NOVELTY - Method of treating **tumors** in the body in communication with arterial and venous blood flow in which a substantial portion of **cytotoxic** drug is infused into the **tumor** and prevented from diffusing into the body.

DETAILED DESCRIPTION - Method of treating **tumors** comprises:

(a) mapping surface and volume of the **tumor**;

(b) locating arteries upstream of the **tumor**;

(c) calculating optimum, controlled dose of **cytotoxic** drug suitable for treating the **tumor**;

(d) infusing controlled dose of **cytotoxic** drug into the **tumor** from one or more of the arteries at select locations upstream of the **tumor**; and

(e) withdrawing blood from one or more veins at select locations downstream of the **tumor** for extracorporeal treatment to remove the **cytotoxic** drug from the withdrawn blood, such that a substantial portion of the **cytotoxic** drug is infused into the **tumor** and prevented from diffusing into the body.

ACTIVITY - **Cytotoxic**; anti-**tumor**.

USE - The method is used to treat **tumors** in the body in communication with arterial and venous blood flow (claimed). The method is also used to treat hyperproliferative disease including cancer, using real-time computer control to visualize, position and operate drug-infusion and imaging devices within the body of the patient.

ADVANTAGE - The method allows precise, real-time computer control of the point or points of drug delivery within the body of a patient. The method also provides method that reveals diffusion of **cytotoxic** drugs throughout an area of diseases or abnormal tissue. The method also allows delivery and control of diffusion within the body of **cytotoxic** drugs by manipulation of local blood flow patterns through the point injection of vasoconstricting and/or vasodilating drugs.

DESCRIPTION OF DRAWING(S) - The drawing illustrates how progression of tagged **cytotoxic** drug can be monitored through **tumor** and its diffusion controlled.

primary **tumor** 53
basement membrane 54
normal epithelial cells 55
artery 56
arterioles 57
capillaries 58
vein 59
infusion catheter 60
withdrawal catheter 61
withdrawal openings 62
injection openings 63
Dwg.4/4

L24 ANSWER 15 OF 22 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1999-254702 [21] WPIDS
DNN N1999-189600 DNC C1999-074523
TI Processing a lipid membrane bound structure.
DC B04 D16 P34

IN GRAE, J B
PA (IBTW-N) IB2 LLC
CYC 83
PI WO 9915638 A1 19990401 (199921)* EN 75p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
AU 9897753 A 19990412 (199934)
EP 1015571 A1 20000705 (200035) EN
R: AT BE CH DE DK ES FI FR GB GR IE IT LI NL PT SE
US 6277610 B1 20010821 (200150)
ADT WO 9915638 A1 WO 1998-US19815 19980923; AU 9897753 A AU 1998-97753 19980923; EP 1015571 A1 EP 1998-951925 19980923, WO 1998-US19815 19980923; US 6277610 B1 Provisional US 1997-60690 19970923, WO 1998-US19815 19980923, US 2000-508889 20000317
FDT AU 9897753 A Based on WO 9915638; EP 1015571 A1 Based on WO 9915638; US 6277610 B1 Based on WO 9915638
PRAI US 1997-60690 19970923; US 2000-508889 20000317
AB WO 9915638 A UPAB: 19990603
NOVELTY - A method for processing a lipid membrane bound structure comprises:

(1) providing the structure to be processed in a liquid medium; and

(2) heating the liquid medium containing the structure at a rate and through a temperature range sufficient to cause an instability in the structure without lysing the structure.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM has also been included for an apparatus for carrying out the method above, comprising means for ensuring a low average density stream of medium containing the lipid membrane bound structures and associated proteins and means for heating the low average density stream of medium within tightly controlled temperature profile parameters.

USE - The process seeks to alter cell characteristics by a thermal shock process and may be used, for example, to inactivate or kill bacteria (in milk), alter cell surface chemistry or antigenicity, disrupt membranes, activate cell functions or responses, disaggregate cells, as a pretreatment before cell fusion or infection, activate or change the function of a cellular parasite (e.g. bacteria, mycoplasma, virus or prion), affect mitochondrial functioning or the functioning of other organelles. On an organism level, the present invention may be used to treat bacterial infections, such as osteomylitis, viral infections such as AIDS, human or animal Herpes viruses (including HHV-5 and EBV, as well as CMV, HSV-1, HSV-2, VZV, HHV-8, and the like), treat cancer, **sarcoma**, mesothlioma, teratoma or other malignancy or neoplasm, treat skin conditions, such as psoriasis, treat inflammation, treat fungal diseases, blood borne diseases and leukemias. The present invention may also have utility in the treatment of syndromes, which may be multifactorial in origin and involve an immunological component or defect. The process may also find utility in the treatment of chronic fatigue syndrome (CFS), for example by applying immune stimulation therapy through treatment of blood or blood components.

ADVANTAGE - The broad utility of the present 'invention comes from its ability to carefully control a stress applied to a cell. This stress may, of course, kill the cell or selectively kill a subpopulation of cells, but more importantly, it is believed that the present invention may be applied to cells to have a measurable non-transient effect which does not immediately result in cell death. In this manner, the present method provides a new manipulation modality for cells. In contrast to known cellular thermal inactivation methods, the major aspects of the present invention do not rely on thermal denaturation of cellular proteins and enzymes, but rather on a rapid temperature rise which irreversibly changes

the cell, at temperatures and energy levels below those required by traditional pasteurization processes.

DESCRIPTION OF DRAWING(S) - A diagram of a steam condensation reactor vessel.

201 = conduit
202 = steam injectors
203 = upper body
204 = lower body
205 = seal
206 = baffle
207 = vacuum control system
208 = exit port
210 = reactor space

Dwg.0/16

L24 ANSWER 16 OF 22 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1992-258893 [31] WPIDS
CR 1990-140004 [19]
DNN N1992-197519 DNC C1992-115379
TI Delivery of **cytotoxic** radionuclide to nuclei of **tumour** cells - using immuno-conjugate comprising **monoclonal** antibody 17-1A labelled with 125 I.
DC B04 K08 S05
IN MATTIS, J A; STEPLEWSKI, Z; WOO, D V
PA (CENZ) CENTOCOR INC
CYC 1
PI US 5130116 A 19920714 (199231)* 14p
ADT US 5130116 A CIP of US 1988-256655 19881012, US 1990-530091 19900529
PRAI US 1988-256655 19881012; US 1990-530091 19900529
AB US 5130116 A UPAB: 19931123
Delivery comprises contacting the **tumour** cells with an immunoconjugate comprising **monoclonal** antibody 17-1A (or a fragment) labelled with 125I, the **monoclonal** antibody being capable of localising the radionuclide at the **tumour** cell nucleus.

ADVANTAGE - The method allows a **tumour**-lethal dose radiation to be effectively localised at the **tumour** cell nucleus thereby maximising the effect of the radiation at the **tumour** site while minimising radiation **damage** to healthy tissue. The antibody is internalised into the **tumour** cell and the radionuclide is thereby placed in close proximity to the **tumour** cell nucleus. The radiation emitted by the Auger-electron emitter is partic. lethal at this close range to the **tumour** cell, but not to surrounding tissue, due to its subcellular range. The radiation damage to the cells is ultimately due to chromosomal damage which results in irreparable damage to and provides efficient killing of the **tumour** cells.

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11co
Dwg.1a/8

L24 ANSWER 17 OF 22 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1992-017847 [03] WPIDS
CR 1997-309831 [28]; 1997-362934 [33]
DNC C1992-007705
TI New plant ribosome inactivating proteins and inactive precursors - expressed in eukaryotic cells, useful e.g. in **tumour** or HIV treatment, and new DNA encoding them.
DC B04 D16
IN HEY, T D; MORGAN, A E R; WALSH, T A
PA (DOWC) DOWELANCO; (DOWC) DOW AGROSCIENCES LLC
CYC 21
PI EP 466222 A 19920115 (199203)* 40p

R: AT BE CH DE ES FR GB GR IT LI LU NL SE
AU 9178329 A 19911212 (199206)
BR 9102418 A 19920114 (199207)
CA 2044201 A 19911212 (199210)
HU 58800 T 19920330 (199217)
JP 04279599 A 19921005 (199246) 37p
CN 1062172 A 19920624 (199310)
AU 638133 B 19930617 (199331)
US 5248606 A 19930928 (199340) 32p
EP 466222 B1 19990908 (199941) EN
R: AT BE CH DE DK ES FR GB GR IT LI LU NL SE
DE 69131589 E 19991014 (199949)
ADT EP 466222 A EP 1991-201436 19910610; JP 04279599 A JP 1991-139171 19910611; CN 1062172 A CN 1991-104857 19910611; AU 638133 B AU 1991-78329 19910611; US 5248606 A US 1990-535636 19900611; EP 466222 B1 EP 1991-201436 19910610; DE 69131589 E DE 1991-631589 19910610, EP 1991-201436 19910610
FDT AU 638133 B Previous Publ. AU 9178329; DE 69131589 E Based on EP 466222
PRAI US 1990-535636 19900611
AB EP 466222 A UPAB: 19991124
New pure protein, designated proRIP, is (1) unable to inactivate eukaryotic ribosomes but (2) contains an internal peptide linker sequence (LS) which, when removed, converts it into a protein, RIP, which can inactivate such ribosomes. Also new are (1) RIP, having alpha and beta fragments; (2) fusion proteins (FP) including RIP; (3) conjugates of RIP and targetting vehicle; (4) DNA encoding proRIP, RIP and FP; (5) expression vectors contg. such DNA; and (6) host cells transformed with these vectors.

RIP is a Panicoideae; barley; ricin A-chain; saporin; abrin A-chain; SLT-1; alpha-trichosanthin; luffin-A or mirabilis antiviral RIP; and LS is homologous to the sequence MATL(E)4VKMQMQMPEAADL(A)4 (I).

USE/ADVANTAGE - proRIP can be expressed in eukaryotic cells, then converted to active form. Mature RIP catalytically inactivate eukaryotic ribosomes so are very powerful inhibitors of eukaryotic protein synthesis. Potential applications include HIV treament (US4869903) and construction of toxins targetted to specific (**tumour**) cells by attachment to a target polypeptide (**monoclonal** antibodies). @(40pp Dwg.No 0/

L24 ANSWER 18 OF 22 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1991-058150 [08] WPIDS
DNC C1991-024572
TI **Monoclonal** antibodies specific for cathepsin B-like pro enzymes - not reactive with mature enzyme, useful for diagnosing and locating **tumours** etc., and new therapeutic **immuno toxins**
.
DC B04 D16
IN BURTIN, P; FAGANO, M; FONDANECHE, M C; KEPPLER, D
PA (CNRS) CENT NAT RECH SCI
CYC 14
PI WO 9101378 A 19910207 (199108)*
RW: AT BE CH DE DK ES FR GB IT LU NL SE
W: JP US
FR 2649891 A 19910125 (199111)
PRAI FR 1989-9650 19890718
AB WO 9101378 A UPAB: 19930928
New **monoclonal** antibodies (MAb) directed against **protease** precursors are (1) specific for the epitopes of cathepsin B-like proenzymes (PCBL) with no immunological cross-reactivity with the mature enzymes cathepsin B-like, cathepsins B, H and L, or papain; and (2) recognise PCBL epitopes which can differ from one MAb to another. Also new are (1) hybridomas which secrete MAb and (2) **immunotoxins** consisting of MAb plus a toxin.

MAb are of class IgG1-k; have mol. wt. about 150000, and have high

affinity for PCBL.
USE/ADVANTAGE - These very specific MAb (which react with PCBL of mol. wt. 45-47 and/or 36 kD) are useful in diagnosing development of disease, esp. of **tumours** which secrete PCBL, inflammation and immune deficiency. When labelled with a radioisotope, MAb can also be used for scintigraphic localisation of **tumours** and other PCBL-producing cells. The **immunotoxins** are useful therapeutically.
0/0

L24 ANSWER 19 OF 22 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1991-037156 [06] WPIDS
DNN N1991-028836 DNC C1991-015923
TI Method for screening **monoclonal** antibodies - use in treatment of **tumours**.
DC B04 D16 K08 S03
IN KOPROWSKI, H; SCULCZYNSK, E R; RAKOWICZ-SZULCZYNSKA, E
PA (WIST-N) WISTAR INST ANATOMY & BIOLOGY
CYC 2
PI CA 2016830 A 19901116 (199106)*
US 5296348 A 19940322 (199411) 8p
ADT CA 2016830 A CA 1990-2016830 19900515; US 5296348 A US 1989-352258 19890516
PRAI US 1989-352258 19890516
AB CA 2016830 A UPAB: 19930928
Method for selecting a **monoclonal** antibody capable of binding to a cell surface receptor of a selected **tumour** cell, internalising and translocating to the nucleus of the cell, from a gp. of **monoclonal** antibodies capable of binding to the cell surface receptor comprises: (a) incubating each **monoclonal** antibody having a radioactive label, with a sample of the **tumour** cells; (b) fractionating the incubated cells into cytoplasm, nucleoplasm, nuclear **membrane** and chromatin **cell** fractions; (c) detecting the amt. of label bound to each cell fraction; (d) calculating the number of molecules of each **monoclonal** antibody taken up by each cell fraction; and (e) comparing the results of (d) for each **monoclonal** antibody to identify which is translocated to the nucleus and bound to the chromatin.
Also claimed are: (A) a method for selecting a **monoclonal** antibody capable of stimulating a surface antigen on a **tumour** cell; (B) a method for determining the anti-transcriptional and anti-replicational intracellular effect on cell metabolism of a **monoclonal** antibody; (C) a method for determining the therapeutic dosage of a **monoclonal** antibody for treatment of cancer; and (D) a method for treating a **tumour** characterised by an under expressed surface antigen.
USE/ADVANTAGE - Used to identify the most effective antibody acting at the transcriptional level to inhibit **tumour** cell growth or for transporting a radioactive isotope or **cytotoxic** agent into **tumour** cells and for treating cancers with such antibodies and identifying the most effecting dosage. Those antibodies which inhibit **tumour** cell growth may be used therapeutically.a @(44pp Dwg.No.0/0)

L24 ANSWER 20 OF 22 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1989-297800 [41] WPIDS
DNC C1989-131903
TI **Cytotoxic** drugs for malignant **tumours** - contain **monoclonal** antibody against **tumour** growth factor.
DC B04 D16
PA (TOXN) TOYO JOZO KK
CYC 1
PI JP 01221326 A 19890904 (198941)* 11p

ADT JP 01221326 A JP 1988-44350 19880229
PRAI JP 1988-44350 19880229
AB JP 01221326 A UPAB: 19930923
Cytotoxic drugs contain **monoclonal** antibody against **tumor** growth factor or **tumour** activating factor, including TAG insulin, insulin-like growth factors and EGF. More specifically, **monoclonal** antibody against TAG obtd. from TAG-I-1 (FERM P9851) is used as an active component.
In the prepn. TAGI-1 cell is injected intraperitoneally to F1 mice of BALB/C MICE and C57BL/6 mice. After 18 days, the ascite is taken and purified with euglobulin fractionation. AFter column chromatography, **monoclonal** antibody TAG-1 is obtd., which can recognise specifically growth factor, TAG.
USE/ADVANTAGE - In presence of complement and **tumour** receptor binding factor, **monoclonal** antibody against this factor can **damage** the malignant **tumours** and detect the malignant **tumour** cells. With this **monoclonal** antibody, a factor which can bind to **tumour** receptor, complement and **tumour** receptor can be detected.
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L24 ANSWER 21 OF 22 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1989-040641 [06] WPIDS
CR 1992-160671 [20]; 1993-160482 [20]; 1996-499138 [50]
DNC C1989-017739
TI **Cytotoxic** agents for treatment of **tumour** cells - comprising an antibody-enzyme conjugate and a pro-drug, where the enzyme converts the pro-drug into the parent drug.
DC B03 B05 D16
IN BROWN, J P; KERR, D E; SAULNIER, M G; SENTER, P D
PA (BRIM) BRISTOL-MYERS SQUIBB CO; (BRIM) BRISTOL-MYERS CO; (ONCO) ONCOGEN
CYC 27
PI EP 302473 A 19890208 (198906)* EN 60p
R: AT BE CH DE ES FR GB GR IT LI LU NL SE
NO 8803414 A 19890227 (198914)
DK 8804341 A 19890205 (198917)
HU 47437 T 19890328 (198917)
FI 8803597 A 19890205 (198918)
ZA 8805705 A 19890426 (198923)
AU 8820201 A 19890525 (198929)
PT 88187 A 19890630 (198930)
JP 02223532 A 19900905 (199042)
DD 280334 A 19900704 (199048)
US 4975278 A 19901204 (199051)
DD 281962 A 19900829 (199105)
DD 283634 A 19901017 (199112)
HU 207230 B 19930329 (199316)
NO 9400675 A 19890206 (199419)
KR 9306757 B1 19930723 (199427)
EP 302473 B1 19950215 (199511) EN 76p
R: AT BE CH DE ES FR GB GR IT LI LU NL SE
DE 3853028 G 19950323 (199517)
ES 2068191 T3 19950416 (199522)
CA 1336887 C 19950905 (199542)
IL 87319 A 19950831 (199543)
NO 178138 B 19951023 (199547)
NO 178341 B 19951127 (199601)
PT 101702 A 19960131 (199611)
IE 68309 B 19960612 (199641)
FI 98197 B 19970131 (199711)
JP 2738414 B2 19980408 (199819) 38p
JP 10130295 A 19980519 (199830) 35p
IE 80975 B 19990811 (199942)

JP 3127136 B2 20010122 (200112) 34p
ADT EP 302473 A EP 1988-112646 19880803; ZA 8805705 A ZA 1988-5705 19880803; JP 02223532 A JP 1988-194308 19880803; US 4975278 A US 1988-211301 19880629; HU 207230 B HU 1988-4080 19880803; NO 9400675 A Div ex NO 1988-3414 19880802, NO 1994-675 19940225; KR 9306757 B1 KR 1988-9909 19880803; EP 302473 B1 EP 1988-112646 19880803; DE 3853028 G DE 1988-3853028 19880803, EP 1988-112646 19880803; ES 2068191 T3 EP 1988-112646 19880803; CA 1336887 C CA 1988-573684 19880803; IL 87319 A IL 1988-87319 19880802; NO 178138 B NO 1988-3414 19880802; NO 178341 B Div ex NO 1988-3414 19880802, NO 1994-675 19940225; PT 101702 A PT 1995-101702 19950512; IE 68309 B IE 1988-2379 19880803; FI 98197 B FI 1988-3597 19880801; JP 2738414 B2 JP 1988-194308 19880803; JP 10130295 A Div ex JP 1988-194308 19880803, JP 1997-179582 19880803; IE 80975 B Div ex IE 1988-2379 19880803, IE 1995-981 19880803; JP 3127136 B2 Div ex JP 1988-194308 19880803, JP 1997-179582 19880803
FDT HU 207230 B Previous Publ. HU 47437; DE 3853028 G Based on EP 302473; ES 2068191 T3 Based on EP 302473; NO 178138 B Previous Publ. NO 8803414; NO 178341 B Previous Publ. NO 9400675; FI 98197 B Previous Publ. FI 8803597; JP 2738414 B2 Previous Publ. JP 02223532; JP 3127136 B2 Previous Publ. JP 10130295
PRAI US 1988-211301 19880629; US 1987-81382 19870804; US 1988-161068 19880226
AB EP 302473 A UPAB: 20010302
The use is claimed of at least one prodrug i.e. weakly **cytotoxic** to **tumour** cells compared to its corresp. parent drug and of at least one antibody-enzyme conjugate comprising an antibody reactive with an antigen on the surface of **tumour** cells conjugated to an enzyme capable of converting the prodrug into the more **cytotoxic** parent drug, for prepg. a pharmaceutical compsn. for the treatment of **tumours**.

The ensyme may be e.g. alkaline phosphatase, penicillin amidases, arylsulphatases, cytosine deaminases, **proteases**, D-alanyl carboxylpeptidases or beta-lactamases. The prodrug may be e.g. etoposide phosphates, etoposide thiophosphates, etoposide sulphates, teniposide phosphates, adriamycin phosphates, adriamycin sulphates or N7-1-8C alkyl mitomycin phosphates.

Als claimed are anthracycline derivs. of formula (I) (X = -CH2- or -CH2-O-; R1 = H and R3 = OH or OCH3 or R1 = OH and R3 = OCH3 and R2 = H or OH).

USE/ADVANTAGE - The compsns. provide a simple and direct procedure for delivering **cytotoxic** drugs to **tumour** cells, allowing enhanced selective **cytotoxicity** while avoiding the problems of heterogeneous antigen expression, antigen/ antibody internalisation and insufficient drug potency inherent is conventional antibody-directed immunotherapy techniques.
Dwg.0/29

L24 ANSWER 22 OF 22 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1986-157521 [25] WPIDS
DNC C1986-067282
TI New lymphokine, LK 2 and **monoclonal** antibodies - for treating **tumours**.
DC B04 D16
IN KURIMOTO, M; MITSUHASHI, M
PA (HAYB) HAYASHIBARA SEIBUTSU KAGAKU; (HAYB) HAYASHIBARA KEN; (HAYB) HAYASHIBARA SEIBUTS; (HAYB) HAYASHIBARA BIOCHEMICAL LAB; (HAYB) HAYASHIBARA SEIBUTSU KAGAKU RES CO LTD
CYC 12
PI GB 2168355 A 19860618 (198625)* 16p
FR 2572936 A 19860516 (198626)
AU 8549708 A 19860515 (198627)
SE 8505286 A 19860510 (198627)
JP 61115026 A 19860602 (198628)

JP 61115027	A	19860602	(198628)	
JP 61115028	A	19860602	(198628)	
JP 61115099	A	19860602	(198628)	
DE 3539775	A	19861106	(198646)	
ES 8703161	A	19870416	(198719)	
CH 664574	A	19880315	(198816)	
ES 8801582	A	19880416	(198823)	
GB 2168355	B	19890419	(198916)	
IT 1184668	B	19871028	(199041)	
US 5003048	A	19910326	(199115)	
US 5019385	A	19910528	(199124)	
US 5030564	A	19910709	(199130)	
AT 8503276	A	19920115	(199206)	
SE 468853	B	19930329	(199315)	
JP 05023755	B	19930405	(199316)	11p
JP 05032033	B	19930514	(199322)	9p
DE 3539775	C2	19940526	(199419)	19p
KR 9304596	B1	19930601	(199423)	
JP 08011759	B2	19960207	(199610)	10p

ADT GB 2168355 A GB 1985-27466 19851107; FR 2572936 A FR 1985-16536 19851108; JP 61115026 A JP 1984-28396 19841109; JP 61115027 A JP 1984-236356 19841109; JP 61115028 A JP 1985-166754 19850730; JP 61115099 A JP 1984-236357 19841109; DE 3539775 A DE 1985-3539775 19851109; ES 8703161 A ES 1985-548727 19851108; ES 8801582 A ES 1986-556785 19860625; US 5003048 A US 1988-223717 19880721; US 5019385 A US 1985-792158 19851028; US 5030564 A US 1988-223719 19880721; SE 468853 B SE 1985-5286 19851108; JP 05023755 B Div ex JP 1984-236356 19841109, JP 1985-28396 19841109; JP 05032033 B JP 1984-236357 19841109; DE 3539775 C2 DE 1985-3539775 19851109; KR 9304596 B1 KR 1985-8229 19851105; JP 08011759 B2 JP 1984-236356 19841109

FDT JP 05023755 B Based on JP 61115026; JP 05032033 B Based on JP 61115099; JP 08011759 B2 Based on JP 61115027

PRAI JP 1984-236356 19841109; JP 1984-236357 19841109; JP 1985-28396 19850218; JP 1985-166754 19850730

AB GB 2168355 A UPAB: 19931112

Lymphokine (LK2) with the following physicochemical properties is new: (1) mol.wt.: 20000+-2000 daltons; (2) isoelectric pt.: pI=6.2+-0.3; (3) electrophoretic mobility: on Disc-PAGE, Rf=0.29(+-)0.02; (4) UV absorption spectrum: absorption maximum at 280 nm; (5) solubility in solvents: soluble in water, saline and phosphate buffer; scarcely soluble or insoluble in ethyl ether, ethyl acetate or chloroform; (6) colouring reaction: protein-positive by Lowry's method or microburet method; saccharide-positive by the phenol-sulphuric acid method or anthrone-sulphuric acid method; (7) biological activities: **cytotoxic** on L 929 cells and KB cells; free from interferon activity; (8) stability in aq. soln. stable up to 60 deg.C when incubated at pH 7.2 for 30 mins; stable oVer a pH range of 4.0-11.0 when incubated at 4 deg.C for 16 hrs.; (9) stability on cryopreservation: stable at -10 deg.C over a period of one month or longer.

Prodn. of LK 2 by induction of human cells, and **monoclonal** antibodies to LK2 and their prodn. are also claimed, as is purificn. of LK2 by affinity, chromatography.

USE - LK2 shows **cytotoxic** activity against malignant **tumour** cells. LK2 may also be used to enhance antioncotic effects of chemotherapeutic agents, roadening their **tumour** sepctra, as well as enabling treatment of drug-resistant **tumours**. The **monoclonal** antibodies may be used as a ligand for affinity chromatography directed to LK2 prodn., as well as in diagnosis of a variety of human diseases because of their specificity to LK2 which **damages** malignant **tumours**. Dosage is 5-5 x 10 power8 units/day.

Dwg.0/0

```
=> d his

     (FILE 'WPIDS' ENTERED AT 14:21:29 ON 22 OCT 2001)
                DEL HIS Y
L1         31309 S TUMOR# OR TUMOUR# OR CARCINOMA# OR SARCOMA#
L2         10136 S MONOCLONAL
L3          2281 S L1 AND L2
L4          5210 S IMMUNOTOXIN# OR IMMUNO TOXIN# OR CYTOTOX?
L5           371 S L3 AND L4
L6         17044 S LIPASE# OR PROTEASE? OR PROTEINASE#  OR LIPOLYTIC OR PROTEOLY
L7            12 S L5 AND L6
L8         88129 S PERMEAB?
L9             4 S L5 AND L8
L10        12685 S VASCULA?
L11           22 S L5 AND L10
L12          316 S L10 (5A) (INCREAS?)
L13            0 S L11 AND L12
L14         5925 S CELL (3A) MEMBRANE#
L15           16 S L5 AND L14
L16          786 S L14 (L) (WEAK? OR PERMEAB? OR OPEN?)
L17            0 S L15 AND L16
L18          251 S L1 (5A) DAMAG?
L19            1 S L15 AND L18
L20       103106 S PENETRAT?
L21            1 S L20 AND L15
L22            6 S L5 AND L18
L23            1 S L20 AND L14 AND L5
L24           22 S L7 OR L9 OR L19 OR L21 OR L22 OR L23

     FILE 'WPIDS' ENTERED AT 14:42:24 ON 22 OCT 2001

=> d cost

COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
CONNECT CHARGES                                  36.24     222.33
SEARCH CHARGES                                    0.00     178.60
DISPLAY CHARGES                                  60.72     101.21
                                              ---------  ---------
                                                 96.96     502.14
CAPLUS FEE (5%)                                   0.00       2.78
                                              ---------  ---------
FULL ESTIMATED COST                              96.96     504.92

IN FILE 'WPIDS' AT 14:49:40 ON 22 OCT 2001


=> log y
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
FULL ESTIMATED COST                              96.96     504.92

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on the following link to access the survey.
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http://www.cas.org/ONLINE/STN/ExpressSurveyForm.html?LOGINID=SSSPAT01AK

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STN INTERNATIONAL LOGOFF AT 14:49:51 ON 22 OCT 2001

Connection closed by remote host